Report Rapport

RISK ESTIMATES FOR THE HEALTH EFFECTS OF ALPHA RADIATION

by

Duncan C. Thomas and
K.G. McNeill

[redacted]

Atomic Energy
Control Board

P.O. Box 1046
Ottawa, Canada
K1P 5S9

Commission de contrôle
de l'énergie atomique

C.P. 1046
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K1P 5S9

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ABSTRACT

This report provides risk estimates for various health effects of alpha radiation. Human and animal data have been used to characterize the shapes of dose-response relations and the effects of various modifying factors, but quantitative risk estimates are based solely on human data: for lung cancer, on miners in the Colorado plateau, Czechoslovakia, Sweden, Ontario and Newfoundland; for bone and head cancers, on radium dial painters and radium-injected patients.

Slopes of dose-response relations for lung cancer show a tendency to decrease with increasing dose. Our best estimate of curvilinearity is given by raising dose to the power 0.92 ± 0.07, but the improvement in fit beyond simple linearity is not significant. On the other hand, the addition of a cell-killing term significantly improves the fit of the linear model. In any event, linear extrapolation is unlikely to underestimate the excess risk at low doses by more than a factor of 1.5. However, these inferences about curvilinearity are highly subject to error from the choice of reference populations, dosimetry, and latency. Under the linear cell-killing model, our best estimate of excess relative risk is 2.28 ± 0.35 per 100 WLM (a doubling dose of 44 WLM). Attributable risks in these five studies range from 3.4 to 17.8 per 10^6PY-WLM.

Risks from radon daughters appear to interact with age and smoking in a form intermediate between additive and multiplicative, though on balance, closer to multiplicative. We therefore favor the "relative risk model" for projecting lifetime risks, but have carried out life-table projections under a wide variety of assumptions. Our best estimate of the effect of a 50-year occupational exposure to 4 WLM/yr is 130 excess lung cancer deaths per 1000 persons (0.65 per 1000 person-WLM), with a range from 60 to 250 per 1000. Similar calculations for lifetime exposure to an additional 0.01 WL beyond normal background produces an estimate of 10 excess lung cancers per 1000 persons.

Our risk estimate for radium are 2.4 bone sarcomas and 2.0 head carcinomas per 10^5Py-μCi. The lifetime risk from radium in drinking water at the Canadian maximum acceptable concentration is about 0.4 per 1000 persons, compared with a natural risk of 1.0 per 1000; at the target concentraton of 2.7 pCi/ℓ the risk is 0.04 per 1000.

No major health effects of plutonium have yet been demonstrated in human populations, probably because of the small number of persons exposed to significant doses, though animal studies clearly show its carcinogenic potential. Other effects of alpha emitters which have been reported include gastrointestinal, skin, and liver tumors, leukemia, liver cirrhosis, and chromosomal abnormalities, but these require further study before their risks can be adequately described.

RÉSUMÉ

Ce rapport présente dos estimations de risque pour divers effets des radiations alpha sur la santé. On a utilisé des données humaines et animales pour caractériser les formes des relations dose-réponse et les effects de différents facteurs de modification, mais les estimations quantitatives de risque sont baseées uniquement sur des données humaines: pour le cancer du poumon, sur les études de mineurs du plateau du Colorado, de la Tchécoslovaquie, de la Suède, de l'Ontario et de Terre-Neuve; pour le cancer des os et de la tête, sur les études de peintres de cadran au radium et des malades traités par injection au radium.

Les pentes des relations dose-réponse pour le cancer du poumon tendent à décroître avec l'accroissement de la dose. Notre meilleure estimation de la curvilinéarité est obtenue en élevant la dose à la puissance 0.92 ± 0.07, mais l'amélioration de l'ajustement au-delà de la linéarité simple n'est pas significative. D'autre part, l'addition d'un terme de destruction des cellules améliore de façon significative l'ajustement du modele linéaire. De toute façon, il est peu probable que l'extrapolation linéaire sous-estime l'excès de risque pour des doses faibles par un facteur de plus de 1.5. Toutefois, ces inférences sur la curvilinéarité sont hautement soumises aux erreurs provenant du choix des populations de référence, de la dosimétrie et de la période de latence. Sous le modèle linéaire avec destruction des cellules, notre meilleure estimation du risque relatif additionel est de 2.28 ± 0.35 par 100 WLM (une dose qui double 44 WLM). Les risques attribuables dans ces cinq études s'échelonnent entre 3.4 et 17.8 par 10^6PY-WLM.

Il semble y avoir une interaction des risques des produits de filiation du radon avec l'âge et les habitudes de fumer, d'une forme intermédiaire entre la forme additive et la forme multiplicative, bien que dans l'ensemble, elle soit plus pres de la forme multiplicative. Dès lors, nous favorisons le "modele des risques relatifs" pour la projection des risques à vie, mais nous avons calculé des projections pour les tables de vie sous plusieurs hypotheses. Notre meilleure estimation de l'effet d'une exposition professionelle durant 50 ans à 4 WLM/année est de 130 décès additionnels par cancer du poumon par 1000 personnes (0.65 par 1000 personnes-WLM), avec un écart de 60 à 250 par 1000. Des calculs semblables pour une exposition à vie à 0.01 WL en plus de l'exposition normale conduisent à l'estimation de 10 cancers du poumon additionnels par 1000 personnes.

Nos estimations de risque pour le radium sont de 2.4 sarcomes de l'os et de 2.0 carcinomes de la tête par 10^5PY-μCi. Le risque a vie par le radium contenu dans l'eau potable à la CMA canadienne est d'environ 0.4 par 1000 personnes comparativement à un risque naturel de 1.0 par 1000.

On n'a pas encore démontré d'effet majeur du plutonium sur la santé chez les humains, probablement à cause du nombre restreint de personnes exposées a des doses élevées, bien que des études sur les animaux montrent clairement son potentiel carcinogénique. Parmi les autres effets des émetteurs de rayons alpha qui ont été rapportés, on retrouve des tumeurs gastrointestinales, de la peau et du foie, la leucémie, la cirrhose du foie et des anomalies des chromosomes; toutefois, d'autres études sont nécessaires avant que l'on puisse en décrire les risques de façons adéquate.

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CHAPTER 1

HISTORICAL BACKGROUND

1.1 SCOPE OF THIS REPORT

This report was commissioned in September 1980 by the Subcommittee for Risk Estimates of the Advisory Committee on Radiological Protection of the Atomic Energy Control Board of Canada. The basic purpose was to provide estimates of the risks of various health effects among those radiation workers and members of the general public exposed to alpha radiation. Such risk estimates might serve as a basis for evaluating safety standards.

Many reviews have been carried out by national and international advisory boards (notably UN77, ICRP77, BEIR80, NCRP80; see list of references following chapter 9). Our terms of references were broadly similar to theirs, but were focussed specifically on alpha radiation. The reasons for this orientation are threefold. First, the effects of alpha radiation have received less attention in those reports than those of X-rays, gamma rays and beta particles (or "low-LET" radiation, referring to their low rate of energy loss per unit of distance traversed and hence their great penetrating power; see Chapter 3 for further details), probably because of the fewer numbers of people exposed to alpha radiation and the smaller amount of data available to describe their effects. Second, there is continuing discussion about how the effects of low levels of alpha radiation should be estimated. Third, in the Canadian context, possible effects of alpha radiation from members of the uranium and thorium series are of importance. As no human or animal study of manageable size is ever likely to provide direct evidence of the effects of low levels, any such estimates must be based on extrapolation downwards from higher doses. Whereas there is a general consensus that a linear extrapolation is unlikely to underestimate the risks of low-LET radiation (though some feel it may overestimate them), there is no such consensus for alpha or other forms of "high-LET" radiation (principally neutrons).

Specifically, then, our mandate was the following (in parenthesis, we list the chapter headings under which each is discussed):

1. To provide a historical description of early experiences with alpha radiation (Section 1.2).
2. To describe the radiological properties of common alpha emitters and the systems of units and methods of measuring exposure to them (Chapter 3).
3. To provide an overview of the scientific controversy relating to their health effects, including theoretical

arguments (microdosimetry, susceptibility, etc.) which have been brought to bear on the question (Chapters 2 and 3).

4. To review the epidemiological evidence on the shapes and magnitudes of dose-response relations for cancer at various sites. This review is intended both to evaluate critically the reliability of such inferences and to provide a synthesis of the best available data (Chapter 5).
5. To review the experimental animal evidence on the shapes of dose-response relations for cancer and other endpoints (Chapter 6).
6. To review both the human and animal evidence on the role of various potentially confounding or modifying factors. The effects of temporal factors (e.g. age and time since exposure) are particularly important as they bear on how risk estimates ought to be projected beyond the close of observation (Chapter 7).
7. To describe any other somatic or genetic effects of alpha radiation which had been observed (Chapters 5 and 6).
8. To describe the standards, guidelines, and regulations which have been recommended by national and international organizations, and to explain their bases (Section 8.2).
9. To discuss the implications of the epidemiological risk estimates for setting standards and particularly for the adequacy of the standards currently in force in Canada or under consideration (Section 8.2).
10. To identify deficiencies in the present state of knowledge and to propose further studies to remedy these deficiencies (Chapter 9).

To ensure that this review be as independent as possible, we have avoided relying on the reports of the various advisory boards except to orient us to the major points of controversy, to provide us with a starting point for our own literature search, and to indicate where our conclusions might be controversial. Instead we have based our analyses almost entirely on our reading of the original sources, insofar as their published accounts permitted. (We have not attempted to obtain raw data, nor have we been able to obtain all the papers in conference proceedings, books, annual reports and minor journals which we have seen cited.) However, in an attempt to present these data from various sources in a systematic fashion, we have reorganized and in some cases statistically analyzed the data in various ways described in Section 4.2; these reanalyses are hitherto unpublished.

Finally, as this review proceeded, we have become increasingly aware of the fundamental importance of methodological considerations. Sections 4.1, 6.1 and 8.1 in particular address issues of the validity and relevance of the data to regulatory decision making.

1.2 EARLY EXPERIENCES WITH ALPHA RADIATION

The earliest observations of the biological effects of alpha radiation were recorded by Agricola in the Erz mountains of Bohemia in 1516. Later, many miners in the regions of Jackymov (or Joachimsthal, in Bohemia) and Schneeburg (Saxony) were described as dying "in the prime of life" (Pi32) or "in middle age" (Lo44) of an otherwise unusual lung disease, afterwards identified as lung cancer. More than four hundred years after Agricola, these cases were shown to have been caused by the short-lived radioactive decay products (or "daughters") of the gas radon, itself a daughter of the uranium present there. Until around 1960, estimates of the exposure of these miners and of their lung cancer rates were about the only bases available for setting standards for radon levels. The evolution of these estimates and recommendations is described in Appendix C.

With the discovery of X-rays and radioactivity around 1895, other biological effects of high doses of radiation became apparent, including other cancers, epilation, and erythema of the skin. Most of these were associated with low-LET radiation. For alpha emitters other than radon daughters, the first reports concerned luminous dial painters who ingested radium through their practice of licking their brushes to get a fine point. In 1924, Blum (Bl24) gave the name "radium jaw" to an unusual form of mandibular osteomyelitis seen among them, and other forms of "radium poisoning" (Le32) and malignancy (Ma31) began to be recognized. Despite their low penetrating power, these alpha rays can cause damage if the alpha-emitting radionuclides are taken internally by inhalation, ingestion or injection because of their very great rate of energy release over the distance they do traverse. Because of its chemical similarity to calcium, radium taken into the system is deposited primarily in the bone, which therefore receives most of the dose. Thus the health effects of different radionuclides (and even different chemical forms of them) depend on their patterns of application, absorption, deposition and retention. Nevertheless, these patterns are somewhat easier to study in exposed humans or animal models than are their long-term carcinogenic effects. Most of our estimates of the effects of other bone-seeking radionuclides, such as plutonium, therefore derive indirectly from the experience of those exposed to radium: the luminous dial painters, radium chemists and other laboratory workers, and patients who received injections or drank solutions of radium for "therapeutic" purposes (Section 5.2). In addition, patients administered Thorotrast (containing radioactive thorium) as a contrast medium for diagnostic radiology have contributed to our knowledge of the radiosensitivity of other organs to alpha radiation. Except for these groups, few persons have been exposed to sufficient doses of other radionuclides to allow adequate quantification of their carcinogenic effects; the few groups which have been described (with largely negative findings, as expected from their sample sizes and doses) are discussed in Appendix I.2.

The largest single irradiation of any human population (in terms of total person-rems of exposure) occurred in the bombing of Hiroshima and Nagasaki in 1945. Due to differences in the construction of the two bombs, for a long time it was thought that the Hiroshima population might have received part of their dose in the form of neutrons, whereas the Nagasaki dose derived almost entirely from gamma rays. Attempts have been made to separate the effects of these two radiations in order to provide information on high-LET radiation, but this has proved to be difficult and almost certainly incorrect for the reasons described in Sections 5.1.1.6.

In the 1950's, there was a sudden increase in the demand for uranium and a consequent increase in uranium mining, notably in the Colorado plateau of the United States, Czechoslovakia and Ontario. These populations, together with certain non-uranium hard rock miners in Sweden, Newfoundland, Great Britain, South Africa and elsewhere have formed the basis for our more recent estimates of the effects of radon daughters, as described in Section 5.1.

Since about 1925, continuing attempts have been made to set limits for radiation exposure to keep the risks low in comparison with other industrial hazards. The historical development of these standards is described in Appendices B, C and D and is summarized in Table 1.1. We describe the basis of the current standards and our risk estimates based on these standards in Section 8.2.

TABLE 1.1

ANNUAL DOSE LIMITS FOR OCCUPATIONAL WORKERS

Year	Limit (whole body, per year)	Remarks
1925	0.1 TED*	about 25 R / year
1934 1934	50 R (ICRP) 25 R (NCRP)	both intended to correspond to 0.1 TED (see text)
1950	15 rem	Change due to higher penetrating radiation and to much more widespread use of radiation
1956	5 rem	"to lessen...incidence...of somatic damage...considered to result primarily from total body exposure."

* Threshold erethyma dose

CHAPTER 2

OVERVIEW OF THE SCIENTIFIC CONTROVERSY

2.1 NEED FOR DOSE-RESPONSE MODELS

The emphasis of this report is on quantifying the levels of radiation which would produce "acceptable" increases in the risk of cancer and other health effects. The judgement of what constitutes an acceptable risk is a difficult social question which is beyond the scope of this report, but in today's political climate, it is generally deemed to be "small" in relation to the risks encountered in everyday life: for example, occupational risks to radiation workers ought to be no larger than those in occupations which are generally regarded as "safe" (ICRP77). (Additionally, one would like to say that the risks be not added without an equal or greater benefit, if there were any sensible way of comparing the two).

Direct observation of such risks becomes a practical impossibility because the sample size needed to produce reasonably precise estimates increases inversely proportionally to the square of the excess. Thus if an epidemiologic study of 1000 exposed and 1000 unexposed were sufficient to demonstrate a doubling of the risk of some disease over a specified period of time, 10,000,000 subjects would be needed in each group to demonstrate a 1% increase in risk.

For only two types of studies are such comparisons conceivable. First are those of entire populations exposed to different levels of radiation. Studies where the different levels are due to natural background are described in Appendix I.2 but have been largely uninformative, mainly because the radiation effect is swamped by the many other factors influencing disease rates which also vary between geographic regions. Among controlled cohort studies of moderately exposed persons, only the study of atomic bomb survivors even begins to approach a sample size sufficient to quantify excess risks of the order of 10%. The second possible type consists of case-control studies of all cases of a specific disease arising in a large population, where exposure histories are determined retrospectively. No such studies have yet been reported for alpha radiation, though some have been done for low-LET radiation (principally diagnostic X-rays). The principal problem with this approach is the difficulty of retrospectively determining quantitative exposure histories.

For this reason, any estimate of the effects of low level radiation must be based on some form of extrapolation downward from the higher levels at which effects are demonstrable. This extrapolation requires some assumption about the mathematical form of the dependence of risk on exposure, or the "dose-response relation". The development of such mathematical models involves an interplay between theoretical considerations and statistical inference from epidemiological and experimental evidence. These two lines of reasoning are summarized in the sections which follow, with the details described in later chapters and appendices.

2.2 A CONVENTIONAL MODEL OF RADIOGENESIS OF CANCER

A widely accepted model of the carcinogenic process holds that cancer is initiated by either a single genetic change or a series of such changes in the chromosomes of a single cell, causing it to proliferate beyond the control of normal defense mechanisms (No76). These changes are random events, whose probabilities are thought to be influenced by the action of carcinogens. Models of the carcinogenic effect of radiation are therefore usually based on theories of how radiation damages single cells. Of these, the "theory of dual radiation action", (Ke71) is the most widely accepted, and is briefly summarized here and in greater detail in Section 3.2.

The theory is based on a distinction between absorbed dose, D, (the amount of energy absorbed by a macroscopic unit of matter) and the specific energy, z, (the corresponding energy per unit mass in a microscopic area, in this case a cell nucleus or even a strand of DNA). The deposition of energy by high LET radiation (e.g. alpha radiation) occurs in a highly non-uniform manner, most cells receiving zero specific energy while a few receive a large specific energy. If the biologic effectiveness depended linearly on the average specific energy $\overline{z}$, this distinction would have no importance because $\overline{z} = D$. In the dual action theory, it is hypothesized that the basic lesion is the misjunction of pairs of sub-lethal lesions (which might for example be breaks in DNA molecules), the probability of which should be proportional to the mean value of z^2 (this follows from target theory, being the probability of at least two hits on the same nucleus provided these events are rare). The mean of z^2 is given by

$$\overline{z^2} = \zeta D + D^2 \qquad [2.1]$$

where ζ depends on the distribution of specific energy: for low-LET radiation, the specific energy is deposited in a relatively large region so that ζ would be small and the quadratic term would predominate (except at very low doses); for high-LET radiation, large specific energies are deposited in a very small region so that the ζ would be large and the linear term would predominate (except at very high doses).

For large absorbed doses, radiation can produce a variety of effects which could compete with the carcinogenic effect. Obvious effects would be sterilization or killing of a cell. If these events are also occurring at a rate proportional to $\overline{z}$ or z^2, the probability of a malignantly transformed cell surviving to cause cancer can be derived from competing risk theory (Ch61) as

$$R = (a + bD + cD^2)\ \exp(-fD-gD^2) \qquad [2.2]$$

where R is the risk of cancer, D is the absorbed dose, and a,b,c,f and g are coefficients to be estimated from experimental or epidemiological data, a being the natural or spontaneous rate of the effect. This is the basic model which has generally been used for describing radiation effects, though a number of important modifications have been included (Ke78) to allow for the effect of DNA repair mechanisms (which introduce a dose-rate dependence); further details are provided in Section 3.2.

2.3 EMPIRICAL EVIDENCE SUGGESTING A MORE GENERAL MODEL

The model described by equation [2.2] includes a wide variety of shapes of dose-response curves, but all share a common property: at low doses, the effectiveness per unit dose (or slope) is either constant or increases with increasing dose. (In subsequent sections, we shall refer to these shapes as "linear" or "concave" respectively). The mathematical form precludes the possibility of a "convex" relationship at low doses, that is slope decreasing with increasing dose.

A number of epidemiologic and experimental studies of high-LET radiation have seemed to indicate some degree of convexity. These studies are reviewed in detail in Chapters 5 and 6 and several methodological artifacts which might account for these observations are discussed in Section 4.2.1. However, taken at face value, these findings have suggested to a number of authors the need for a more general model which would include the possibility of convexity at low doses. Of the various alternative models, the simplest and most popular is the following:

$$R = (a + bD^c)\ \exp(-fD-gD^2) \qquad [2.3]$$

(where the coefficients b and c now have a different interpretation from those in [2.2]). This model includes both the pure linear and pure quadratic cases of equation [2.2] (with or without the cell-killing term) by setting $c=1$ or $c=2$ respectively and approximates the linear-quadratic form by choosing a value of c between 1 and 2. However, it also allows the possibility of convexity by letting c be less than 1. (In this case, the slope becomes infinite at zero dose, which is unattractive, but it still can approximate any reasonable convex relation having finite slope).

It is important to realize that if the value of f in the cell-killing term is large enough, even the model with $c>1$ can show substantial convexity at moderate doses (say, greater than 100 rems) and this is quite plausible considering the very much greater biological effectiveness of alpha particles. In this report we have attempted to distinguish the explanation of cell killing at moderate doses (f large, $c > 1$) from that of true low-dose convexity $c<1$, f small). In most cases, we found it impossible to choose between the two models on the basis of statistical fits to the available data, but we have found that the risk estimates do not differ appreciably (Section 5.1.2).

A potentially powerful test of the low dose behaviour of a model is a comparison of the predicted risks attributable to background radiation with the "natural" incidence of cancer. Obviously any model which predicts a risk greater than this natural incidence (or even a substantial fraction of the natural incidence if other strong factors have already been identified, like smoking for lung cancer) is untenable. However, even this approach involves assumptions, notably in the determination of the "natural" incidence and in how radiation effects interact with those of other carcinogens. These issues are discussed in Section 8.3.1.

2.4 THEORETICAL CONSIDERATIONS SUPPORTING THE GENERAL MODEL

In view of the difficulty of choosing between models [2.2] and [2.3] on empirical grounds, we seek help from further consideration of theoretical arguments. A number of these, in addition to the cell killing effect described above, have been suggested to support the notion of low-dose convexity.

2.4.1 Overkill

Once a cell has undergone malignant transformation, further radiation is probably "wasted". This leads to a non-linear relation for the probability of transformation of the form $(1-e^{-bD})$ which converges to 1 at high doses. As cancer rates rarely approach unity except in animals exposed to extraordinarily high doses, this form reduces to bD at low to moderate doses. If, however, we assume that only a small fraction p of transformed cells become cancerous, then the form

$$R = p(1-e^{-bD}) \qquad [2.4]$$

can become convex at moderate doses, converging to c at high doses.

2.4.2 Variation in susceptibility

This argument can be taken one step further by assuming there is heterogeneity in the susceptibility of the population at risk. Baum (Ba73) considers a population of individuals each of whom has a characteristic (but probably unknown) threshold $D_{1/2} = \ln(2)/b$ at which half will develop cancer. If these thresholds have some distribution f(b), then the resulting population dose-response curve will have the form

$$R(D) = \int_0^\infty f(b)\ (1-e^{-bD})db \qquad [2.5]$$

For the case where f(b) is given by $D_{1/2} = 1$ rem for 1% of the population, 100 rem for 10% and 10,000 rem for 89%, he shows that equation [2.5] can be approximated by model [2.3] where c = 1/2 over the range 1-100 rem. This argument is considered in greater detail in Appendix F; it could equally apply to variation in susceptibility between cells within an organism.

2.4.3 Simultaneous multiple events

In the multistage model of carcinogenesis (Ar60), it is assumed that at least one cell must pass through a particular sequence of k transformations before it begins to proliferate beyond control. (or that k "keys" must be turned in the nuclear lock before it acts in a particular way). Two predictions of this model are that cancer rates would vary as the (k+1) power of age (which is in good agreement with observational data for a wide range of cancers with k usually between 5 and 7) and that dose-response relations would be proportional to D^m where m is the number of transitions influenced by the carcinogen. In various experimental studies, it has been noted that the radiation-exposed animals show rates varying by a lower power of age (typically 3 or 4), suggesting that one or more stages in the natural carcinogenic process have been skipped. A variant of the multi-stage model (Ba76) therefore suggests that radiation acts by causing two or more transitions to occur simultaneously, so that risks would vary as a lower power of age; it can then be shown that the dose-response relation would depend on a power of dose less than unity.

2.5 MODIFYING FACTORS

So far this discussion has considered only the direct interaction between an absorbed dose of radiation and biological effects at the cellular level. Many other factors may modify the relationship between exposure and risk of cancer. In the first stage, obviously the relation between exposure and absorbed dose will depend on many factors such as the mode of intake, absorption, and deposition, all of which will vary between radionuclides and chemical forms. Similarly, smoking may produce a thick mucus layer which absorbs most of the alpha rays. Next, there may be mechanisms of mutation other than the presumed "dual action" model, and dose rate, fractionation, protraction and age of exposure may influence these transformation rates. Malignant transformation of a single cell may not be sufficient to cause cancer, as several contiguous cells may have to be affected or host defense mechanisms impaired. Smoking and other carcinogens may alter the process in various ways, by acting synergistically in initiating the process or promoting an already initiated process. Finally, even if, despite all these other factors, the biological relation between exposure and risk can still be characterized by models [2.2] or [2.3], the apparent relation in an epidemiologic study may differ due to incomplete follow-up, latency, inappropriate comparison, poor dosimetry, inclusion of "wasted doses" in the latent period, or the many other methodologic issues discussed in Chapter 4. The observational evidence on the effects of those modifying factors by which data are available is considered in Chapter 7.

In view of all these complexities, we take the view that model 2.3 is a general form which includes most of the possible relations likely to be encountered and which has some theoretical basis. However, we do not feel that conclusions about biological mechanisms can justifiably be based on statistical fits of the model to epidemiologic data. Its principal value is thus as a data reduction tool and as a tentative means of extrapolation and projection.

CHAPTER 3

PHYSICAL PRINCIPLES

3.1 INTRODUCTION

Absorbed radiation dose, measured in rads or grays, (see Appendix A) is a measure of the energy of radiation deposited in a defined mass of tissue (gram or kilogram). In the case of isotopes such as potassium, which are fairly uniformly distributed in the body and which emit long range gamma and beta rays, the application of such a concept to a practical case is straight-forward. For the alpha emitters, which deposit their energy in a very localized region, the appropriate mass to use is not so obvious. Is it the mass of the very small volume in which the energy is originally deposited, or is it a larger mass? This matter is looked at in detail in Section 3.2. The situation is made more complex for those alpha emitters which are part of a chain of radioactive materials, each of which may be metabolised differently, and each of which may thus give up their energy in different parts of the body. The situation with daughters of the gases radon or thoron is again complicated by the fact that the daughters may either be produced externally to the body and inhaled "pre-formed" or be "born" in the body from an inhaled radioactive parent. Depending on the state of attachment of the daughters on dust particles, they may be trapped at different parts of the respiratory system, not all of which need to have the same radio-sensitivity. Some of the above points relating to radon and its daughters are discussed in Section 3.3.

3.2 ALPHA IRRADIATION AT THE MICROSCOPIC LEVEL

As the range of alpha rays is so short, the deposition of their energy must be considered at the microscopic level as well as at the gross organism level.

In soft tissue, a 5 MeV alpha particle has a range of 40 μm. Its linear energy transfer is thus about 125 keV/μm. As roughly 33 eV are on average dissipated per ion pair (ip) produced, this LET corresponds to approximately 3800 ip/μm. In a cell of diameter 10 μm, this would mean 1250 keV/cell. Taking a cell nucleus as having a thickness (diameter) of about 3 μm, this amounts to 375 keV or 11,000 ip per nucleus. At an even more microscopic level, taking the width of a thread of DNA as 12×10^{-4} μm, this gives 0.15 keV or 4.5 ip per width.

The ionisation caused by the alpha particle is initially produced within a track whose width will not exceed a few atomic diameters, as the charge of the alpha will be screened by a few atoms. Ninety percent will remain within this distance and in material of density 10^3 (kg/m^3) this may amount to a containment in a cylinder of roughly 0.01μm diameter (10% of the ionisation may be present to 0.2 μm) (EPA76). A cylinder of soft tissue of diameter 0.01 μm and length 40 μm has a volume of 3×10^{-15} cc and a mass of the same number of grams. Then the "dose" to this volume given by one 5 MeV alpha particle is 3×10^{7} rads (5 MeV per 3×10^{-15} g). Averaging the energy over the volume of a cell nucleus, the "dose" to a nucleus through which an alpha ray passes is 300 rads and averaging over the volume of a whole cell about 20 rads. Now if we arranged that a group of cells were irradiated such that one alpha particle passes through each cell (which in principle could be done if the alpha particles were regularly spaced on a grid of spacing equal to the cellular diameter) then the average dose would be 20 rads throughout a layer of thickness 40 μm (the range of the alpha particles). For each of the 4 cells traversed by each alpha particle, the probability of hitting a nucleus would be $(3\ \mu m)^2/10\ \mu m)^2$ or 9%; the probability that any of the four nuclei is hit by a single alpha particle is then about $1-(1-0.09)^4=31\%$ in this case of an average dose of 20 rads. In any one of the hit nuclei about 4 ip would be deposited in each strand width of DNA. Such a deposition of energy (300 rads to the nucleus) is sufficient to kill a cell. (Munro (Mu70) finds that doses in the range 30-300 rads delivered to the nucleus of Chinese hamster fibroblast cells were sufficient for 60% of cells to be incapable of survived reproduction, 30% had reduced capability and only 10% (actually 1/13) were unaffected. Considering the wide range of dose, it is not unreasonable to assume as a first approximation that the dose at the high end of the dose is sufficient to kill a cell).

The situation may be briefly contrasted with that for beta rays. Here the LET is some 100 times lower, and correspondingly there is only a 4.5% chance of an ion pair being produced in a strand of DNA. Bombardment of tissue by beta rays on a 10 μm grid spacing would give a dose of 0.2 rads because of the longer range (and correspondingly lower LET), however, there would still be a 9% chance of any one nucleus being hit by a beta ray. While on average at low doses there is little chance of any one strand of DNA being hit (that is, an ion pair being produced in it), a hundred times as many nuclei are at risk with beta rays than with alpha rays of equal energy - the product (ip per strand) × (number of strands hit) is the same for alpha rays and beta rays.

If biological effects depended simply on the probability of a single ion pair being produced in a strand of DNA, with that deposition being followed by irreversible consequences, it would follow that alpha and beta rays of the same energy would produce the same effect (at least to a reasonable first approximation). This is contrary to experience (as described in Chapter 5 and 6) and leads to such hypotheses that (1) there must be multiple "hits" in any one strand of DNA which either sequentially "turn keys" in a mutation process or overwhelm the defence mechanisms of the cell, or (2) there must be effects in neighbouring cells which then interact with one another. In either of these cases, beta rays will clearly be at a great disadvantage for producing damage compared with alpha rays, because the chances are extremely small (16×10^{-4}) either that two events would take place in the same strand of DNA, or that energy would be deposited in the same strand by two independent beta rays which just happened to cross the same nucleus (or contiguous ones under the second hypothesis).

From the point of view of dose-response curves, these hypotheses lead to interesting predictions. Consider the alpha ray case first: as it is highly likely that any ray will create at least one ip per DNA strand, there will be damage by each ray passing through a nucleus; the total damage will then be proportional to the number of such alpha rays, and thus to the gross absorbed dose. On the other hand, with beta rays (and with any other low-LET radiation) the effect may depend either linearly on dose (reflecting the chance of two hits from a single beta ray), or quadratically (reflecting the chance of spatial coincidence of two rays) or both. One would expect the quadratic term also to be dependent on dose-rate as there would probably be a maximum time after the turning of a key beyond which a second hit would be ineffective for turning a second key, that is, because the effects of the first hit may be repairable in a finite time. If the dose rate is low, the probability of a second hit occurring in this time is reduced.

A problem that arises with these simple models is that although a nucleus must be able to reproduce for a cancer cell to replicate, any nucleus through which an alpha particle passed would seem to be so damaged that the cell could not survive (with the caveats noted above); thus it would seem that alpha radiation could not cause cancer. As this conclusion is contrary to experience, some extra sophistication must be introduced; two possibilities are that glancing hits on the nucleus by the alpha ray track might damage but not destroy the nucleus, and that a hit in the cytoplasm can cause nuclear damage by migration of toxins. The former would reduce the chance of carcinogenic interaction by the ratio of $\pi/4 \times 3^2$ to $3\pi \times .01$, a factor of 10^2, but would not alter the basically linear shape of the dose-response curve. However, it must also be noted that subsequent passage of a second alpha particle through a nucleus that has already become cancerous (or precancerous) may sterilise the cell and so eliminate its contribution to the overall clinically manifest cancer risk. This will introduce a negative exponential term into the dose-response relationship, the so called "cell-killing term" (this, of course, applies to low-LET radiation as well). Though neither of these two extra pieces of sophistication will affect linearity at low doses, the cell-killing term will introduce an increasing degree of convexity to the dose-response curve at high doses ($c<1$). As noted earlier, 20 rads (averaged over the cell) may result in a killing dose to 9% of the nuclei at risk, and therefore at 100 rads or 2000 rem cell-killing effects might reduce the carcinogenic effect to 60% of what would be expected under linearity. This may correspond to a few hundred WLM using the relationships discussed in Section E1.5.

In summary, one would expect that at low doses the dose-response curve for high LET radiation would be linear if the epidemiological problems discussed in Chapter 4 are properly dealt with and if the population at risk is homogeneous; at high doses however a downward curvature is almost certain to be evident due to "overkill" and to "cell-killing". There is no obvious boundary at which one will go from "low" to "high" dose.

3.3 RADON AND ITS DAUGHTERS

Radon, a chemically inert gas, is produced by the decay of radium-226 (half-life 1620 years, itself one of the decay products of the uranium series, see Table 3.1). If produced in rock ore, it may diffuse to a free surface and then escape into the air. The "emanation power" of the rock surface will depend largely on its degree of fracturing. At this point, the radon becomes mixed with the rest of the air. As it has a half-life of 3.8 days (Table 3.1), most of the radon produced will be swept out from any enclosed but ventilated space into the open air. The equilibrium level of radon in a mine will then depend on the rate of turnover of the air. The radon left may decay in the mine air, producing RaA (Table 3.1). This is comparatively short lived, and may itself decay to RaB; subsequent decay of the members of the radioactive chain may give rise to RaC, RaC' and RaD, the last a long lived lead isotope. As far as air in the mine is concerned, the chain may be broken at any stage by removal of radioactive material by ventilation, (obviously the decay process will still continue, but will take place elsewhere, now at negligible concentrations).

It is in fact the short lived daughters of radon which pose the greatest health concern, rather than the radon itself. Neither total radioactivity nor even alpha activity are then the most important parameters in describing the health physics status of air in a mine, as radon will be the biggest single component of activity. A better parameter is the alpha energy which will, in the course of time, be emitted by the short lived daughters contained in a litre of the air to which the miner is exposed; the unit of this exposure rate is the Working Level (WL), and the integrated exposure unit the Working Level Month (WLM) (see Appendix C for definitions). Thus the air contains a mixture of radon and its daughters, the proportions depending on the "age" of the air (i.e. the average time since the radon emanated from the rock), which itself is a function of the mine's ventilation rate. Furthermore, the proportion of daughters which exist as free ions or which are attached to aerosols also depends on the age of the air.

This mixture may then be breathed by a worker in a quantity which depends on such factors as the size of his lungs and his breathing rate. The radon itself will be largely exhaled, with only small fractions being dissolved in the blood or decaying while in the lung. Daughters attached to large aerosols may get trapped in the nose or pharynx; free ions have a high probability of becoming attached to surfaces of the bronchii.

Wherever trapped, there is a possibility that the daughters will be translocated either by direct absorption into body fluids or by ciliary action driving the particles to a place where they can be swallowed into the gastrointestinal tract. The short lived daughters are however likely to decay *in situ*, giving their energy and that of subsequent short lived daughters to the surrounding tissue.

Due to the trapping on lung surfaces, and to the short range of the alpha particles emitted by RaA and RaC', the cells just below the surface of the bronchii receive much of the energy and thus the greatest dose. This layer contains rapidly dividing stem cells, which may be particularly sensitive to carcinogenic effects of radiation. Their sensitivity may also be affected by other environmental factors - thus if these factors increase the rate of cell division by damaging the surface cells the carcinogenic sensitivity of the basal layer may be increased.

Attempts have been made to establish a relationship between exposure in WLMs and dose equivalent to lung surfaces in rems in two ways. One approach uses various theoretical models of lung action and of deposition and translocation of trapped daughters (Appendix E). Due to the complexity of the interactions, any figure derived in this way can only be a gross approximation; a reasonable range of values that have been proposed is 1-20 rem/WLM (see Appendix E). This is the equivalent dose to lung tissue - the lower end of the range being for pulmonary tissue and the higher to basal cells in the bronchial region. The (weighted) effected equivalent dose to the whole body is probably within the range 0.3 to 1.0 effective rem/WLM. These figures are for radon daughters; for thoron daughters the calculated relationship between effective equivalent dose and WLM(thoron) or WLM(Tn) is similar - a value of 0.3 rem/WLM(Tn) is recommended by Jacobi et al. (Ja80), and between 0.2 to 0.6 rem/WLM(Tn) by James et al. (Ja81a). As detailed elsewhere (Appendix E) the distribution of dose is very different from radon and thoron daughters. The other approach is based on epidemiological evidence of an equivalence between the biological damage resulting from a "known" WLM and that resulting from "known" rem (in some other setting). Once again such a derived figure can only be crude.

We recommend that for radon daughters a value of 0.8 rem/WLM be used for the relationship between effective dose equivalent and potential alpha activity when dealing with radon daughters, and 0.4 rem/WLM(Tn) for thoron daughters. We do not believe that such values are precise, but that the true value is not likely to be greater than three times or less than one third the quoted values.

3.4 DOSIMETRY

3.4.1 General

In normal health physics practice, radiation doses integrated over some appropriate time are measured by the physical or photochemical effects of the radiation on the ionisation of air (or other material), on the lattice structure of particular crystals (thermo-luminescent dosimeters), or on the production of latent images on X-ray film. For one reason or another, none of these methods have been directly used in situations discussed in this report.

3.4.2 Japanese Bomb Survivors

In the case of the atomic bomb survivors, post-facto estimates have had to be made based on knowledge of energy released by the bomb, its construction, on distance from the centre of the explosion and on the degree of shielding. Great efforts have been made to obtain best possible estimates of these individual doses, using all information, computer calculations and trials at later bomb tests using dosimetric equipment. These efforts include fixing the position of the individual at the time of the bomb with respect to the bomb's point of explosion and with respect to environmental shielding, calculation of the shape of the air-dose curve with distance using weapons testing, normalisation of this to the actual bomb yield, estimation of environmental shielding and of self-shielding of the body for internal organs and estimation of secondary effects due to fall out or local induced activity. These estimates of dose have been made for some 80,000 bomb survivors. Despite these massive efforts, the dosimetry must remain in considerable doubt particularly in so far as it concerns this paper. One of the clearest reasons for this is that at Hiroshima the dose due to neutrons was up to recent times thought to be a significant fraction of the total dose (~25%, with ~75% due to gamma rays), with the fraction itself changing with distance and protection. In this paper, where the main interest is in high LET radiation (which includes neutrons), the Hiroshima data combined with the Nagasaki data (99% gamma) in principle should be able to give useful information on the effects of neutrons. However, there is now considerable uncertainty with respect to neutron doses at Hiroshima (Lo80). Moreover, uncertainty of the estimation of a neutron dose equivalent contribution resulting from subtraction of the large gamma component, coupled with the uncertainties of translating from rems to WLM, make direct comparison with other studies of high LET radiation difficult; here we use the Japanese data simply for information on the shape of the dose-response relationship.

3.4.3 Internal Radium or Thorium

Dosimetry of radium or thorium or other alpha emitters in the body depends on calculations based on estimates of isotope burden in organs as a function of time. Such estimates are based, for instance, on animal studies of the deposition and translocation of the injected isotope and its daughters with time; autopsy data from humans can validate the use of animal data for human studies. The retained dose (RD) of radium can be represented over long time spans (tens of years) by a power function of the time of the form $RD=a(t-\epsilon)^{-b}$ where b is a positive number and ϵ is needed in order to keep RD finite as t goes to 0. The power function may be regarded as the sum of a large number of exponential terms corresponding to the physiological pools in the body wherein radium may reside. After long times, equilibrium will be established throughout the body, and the retention will then decay with a single exponential term. A fuller representation is then a product of power function and exponential terms.

When a viable physiological model has been accepted, knowledge of nuclear data schemes and data on total body burden of any one of the daughters will make possible full estimation of integrated dose. Whole body counting of gamma rays from RaC or ThC, for instance, would suffice for this (Tables 3.1 & 3.2). Measurement of radon or thoron may also be used, but estimation then depends strongly on the fraction of these gases emitted being exhaled (but indeed, any measurement on an isotope far down the radioactive series, such as RaC' or ThC", depends on "wash-outs" of precursor isotopes being normal). Urine assays suffer from the same dependence on a normal biological excretion rate constant.

In practice then as much data as possible should be collected in life; after autopsy of persons with internal contamination, recalculation can be made to bring about full internal consistency of the excreted and retained activities of all the daughters within a framework of the physiological model based on animal and earlier human data.

3.4.4 Radon and Radon Daughters in Air

Budnitz (Bu74) summarised dosimetry techniques, classifying techniques into 4 categories: measurement of radon concentrations in mine air, of radon daughters taken as a whole, of individual radon daughters, and personal dosimeters.

3.4.4.1 Radon. Radon and its daughters may be separated by flowing air through a filter; the inert gas radon passes through it and the daughters are (to a large extent) retained. A radon gas sample may then be collected and put in a vessel, called a Lucas chamber, whose inside is coated with ZnS except for one face which sits on a photomultiplier. Alpha activity builds up on the chamber until equilibrium is reached between radon and its daughters (some few hours). By calibrating the chamber with a known source, measurement of alpha activity then gives radon concentration in the sampled air. Sensitivities of 10 pCi/l are readily obtained and down to 1 pCi/l is possible.

If mine air is sampled without filtration and left for a few hours before measurement, all the alpha emitting radon daughters originally present in the air will have decayed away and the activity measured in the Lucas chamber will be proportional to the radon level.

3.4.4.2 All Radon Daughters. Initial alpha activity on the filter described in Section 3.4.4.1 will be due to RaA and RaC'. After some tens of minutes, the original RaA will have decayed, and all the alpha activity will be due to decay of RaA, B and C to RaC'. By correctly judging the interval between collection and counting, a measure of total potential alpha energy (i.e., WL) can be produced which is largely independent of the initial ratios of the daughters. In the Kusnetz method (Ku56), the count rate per minute is measured by an alpha sensitive device after a delay of 40 minutes (though some have recommended other intervals). The precision is about ±15% at 0.3 WL; as the measurement error is due to Poisson statistics, it improves at higher WL. The device may underestimate WL by 25% if very young air is sampled.

3.4.4.3 Specific Radon and Thoron Daughters. More information on daughter ratios can be obtained if an alpha spectrometer is used which is capable of resolving the RaA and RaC' alpha rays or by observing the decay and build-up of these rays, separate concentrations of RaA, B and C may be estimated.

More information is required if an appreciable concentration of thorium is present because of the different nuclear half-lives of the thorium and radon daughters. On the one hand, more alpha energy channels can be used; alternatively measurements made some hours after collection of samples will give information on thorium A and B (the latter having a half-life of 10 hours), by which time all the radon daughters will have decayed. Recently there has been a review of methods for thoron daughters detailing optimal times (Co81).

3.4.4.4 Personal Dosimeters. These may be carried by individual miners. Most so far depend on a pump and filtering system, and are not entirely reliable under field conditions. A new method, based on the use of permanently charged electrets appears to show promise (Ko81).

3.4.4.5 Working Level Months. Measurements of integrated exposures in units of WLM (unless assessed by personal dosimeter) depend on proper measurement of WLs in all parts of a mine occupied by a worker and proper knowledge of the time he spent in each part. The latter factor is a potent source of error in both current and past calculations of WLM.

However, estimated values of WLM in the past depend also on average WL estimates which are certainly open to question. First of all it must be realized that not until the early 1950's were radon daughters known to be a prime hazard and therefore to be measured. Secondly, the number of measurements made was very small. As an example, Lundin et al., (Lu71, p.31) state that "For the entire 1951-1963 period, 43,000 measurements of radon daughter concentrations were available to characterize the approximately 2,500 uranium mines...", i.e., on average, one and a half per year per mine. Furthermore (Lu71), mine

> "inspectors tended to sample most frequently in those mines and sections of mines thought to have the highest levels... [This] tended to yield radon daughter values greater than would have been obtained by sampling all work areas with equal frequency... In contrast, measurements available from mining companies after 1960 might have yielded low radon daughter values as reports of elevated values may have been minimized to avoid regulatory action. To assure a consistent direction of bias, i.e., over-estimation of radon daughter levels, efforts were made to exclude company measurements data after 1960 from use in epidemiological study of uranium miners"

Lundin et al. also conclude (p. 112) that "miners are more likely to have been misclassified into higher WLM brackets than into lower ones" (and as a result the derived slope of the dose-response curve may be too low).

In addition to the above problems, one notes that breathing rates and environmental factors (e.g., humidity and aerosol size) affect the WLM-dose relationship (Section 7.5 and Appendix E.4).

In view of the above, it is to be not in the least unexpected that dose estimations will vary widely from mine area to mine area, and that therefore slopes of dose-response curves will vary. On the other hand, it is noted that for instance attempts were made in Colorado to keep biases consistent, and that therefore the shapes of a dose-response curve obtained from any one study (convexity or concavity with dose) might be expected to be valid; on this basis comparison of such slopes obtained from different studies may be valid although the individual slopes are not properly comparable.

TABLE 3.1

THE URANIUM SERIES

Nuclide		Half-life	Mode of decay (maximum energy, MeV)
U-238		4.5×10^9 y	α (4.3)
Th-234		24 d	β (0.26)
Pa-234		1.2 m	β (2.3)
U-234		2.5×10^5 y	α (4.9)
Th-230		8×10^4 y	α (4.8)
Ra-226		1620 y	α (4.8)
Rn-222	(Radon)	3.8 d	α (5.6)
Po-218	(RaA)	3 m	α (6.1)
Pb-214	(RaB)	27 m	β (1.0)
Bi-214	(RaC)	20 m	β (3.3 + strong γ)
Po-214	(RaC')	160 μs	α (7.7)
Pb-210	(RaD)	22 y	β (0.06)
Bi-210	(RaE)	5 d	β (1.2)
Po-210	(RaF)	138 d	α (5.3)
Pb-206	(RaG)	∞	- -

TABLE 3.2

THE THORIUM SERIES

Nuclide	Half-life	Mode of decay (maximum energy, MeV)
Th-232	1.4×10^{10} y	α (4.1)
Ra-228	6 y	β (0.06)
Ac-228	6.1 h	β (2.1 + strong γ)
Th-228	1.9 y	α (5.5)
Ra-224	3.6 d	α (5.8)
Rn-220 (Thoron)	54 s	α (6.3)
Po-216 (ThA)	0.16 s	α (6.8)
Pb-212 (ThB)	10.6 h	β (0.6)
Bi-212 (ThC)	1 h	β (2.25) to Po-212, 67% α (6.1) to Tl-208, 33%
67% Po-212 (ThC') 33% Tl-208 (ThC")	0.3 μs 3.1 m	α (8.8) β (2.0 + strong γ)
Pb-208 (ThD)	∞	- -

CHAPTER 4

EPIDEMIOLOGICAL PRINCIPLES

In this chapter, we summarize the basic principles of estimating risk in relation to exposure in human populations and the criteria which we used to judge the reliability of such data. We also describe the adjustments which we performed on the various data sets to try to express them in comparable form and the statistical methods used for fitting dose-response models to these data and for projecting these risks beyond the end of follow-up to a total lifetime under various exposure scenarios.

4.1 EPIDEMIOLOGICAL METHODS FOR RISK ASSESSMENT

4.1.1 Measures of Risk

Risk is defined as the probability of an event, such as disease onset or death, occurring during a defined interval of time (McM70). Its definition in relation to time distinguishes it from *prevalence*, which is the probability of being in a state, such as sickness, at a particular instant. Risk is commonly estimated by dividing the number of events (D) by the initial population at risk (N), and is thus closely related to a *rate* (R), which is the number of events divided by the person-years at risk (PY, the product of the number of subjects at risk and the average length of the interval, or equivalently the sum over all subjects of their times at risk). The relation between risks and rates is discussed further in Appendices J, L and M.

Since the endpoints under study here can be caused by many factors and occur in the apparent absence of exposure, it is useful to have measures of the component of risk which is associated with exposure. Two such measures are commonly used. *Attributable risk* (AR) is the difference in rates between exposed (E) and unexposed (NE) populations i.e. $AR = R_E - R_{NE}$; this difference is commonly called the "absolute risk" in the radiological protection literature, but the former term will be used here to avoid confusion with the preferred epidemiological use of absolute risk as simply the rate in a particular group. *Relative risk* (RR) is the ratio of the rate in the exposed to that in the unexposed, i.e., $RR = R_E/R_{NE}$. Both attributable and relative risk can be defined for subgroups of those exposed at different levels and both require some estimate of the rate in the unexposed, which can come either from the general population or from those minimally exposed in the study group.

For making comparisons between groups exposed at different levels, it is convenient to express risks in units of exposure. The *attributable risk index* (ARI) is defined as the attributable risk divided by the mean exposure (D) of the group, i.e. $ARI = AR/D$. Similarly the *relative risk index* (RRI) is defined as the excess relative risk divided by the mean exposure, i.e.

RRI = (RR - 1)/D. A useful feature of these indices is that if the rate depends linearly on exposure and converges to R_{NE} at zero exposure then both indices will be constant across exposure groups. Where the context is clear, we use the terms effectiveness or slope interchangeably to refer to these indices.

For expressing the results of any study, the choice between the two indices is merely one of convenience. However, in predicting the total risk to a population followed for an entire lifetime, the use of any such index implies a strong assumption about how exposure-induced risks vary with age. This issue is discussed further in Section 4.2.2 and Appendix M.

An issue of particular concern in this report is whether risks do indeed depend linearly on dose. As this will be a recurrent theme, we must pause here to define some terminology. figure 4.1 illustrates three general shapes of dose-response curves which might arise, all characterized by the equation $AR=D^c$. If $c = 1$, we get a linear relationship. For curves with $c > 1$ (or any form in which risks per unit dose increase with dose) we shall use the term concave. For curves with $c < 1$ (or any form in which risks per unit dose decrease with dose) we shall use the term convex. While not perfectly clear, we feel these terms, which are standard usage in calculus, are an improvement on "curvilinear upwards or downwards", "sublinear or quadratic" or any of the other terms we have encountered.

4.1.2 Study Designs to Assess Risk

4.1.2.1 Type of study. Clearly the estimation of these risk indices requires the measurement of both exposure and risk in a group of subjects. Because risk is defined in relation to an interval of time, this can only be accomplished by a longitudinal study. These fall into two basic types (McM70): case-control studies, in which affected and non-affected subjects are selected and compared in terms of their past exposures, and cohort studies, in which exposed and unexposed subjects are selected and compared in terms of their rates of subsequent outcome events. Cohort studies can in turn be subdivided in two dimensions: (1) into historical, in which both exposure and outcome have already occurred before the start of data collection, or concurrent, in which events (and possibly further exposure) are observed during the course of data collection; and (2) into true cohort studies, in which both the outcome events and the population at risk is known, or proportional mortality studies, in which only the outcome events are known, and their distribution by cause of death is compared with that in the general population. The majority of studies of radiation effects have been of the true historical cohort type, though all of other variants have been used.

4.1.2.2 Choice of population. For study of radiation effects, four types of populations have been used: occupationally exposed workers, patients receiving radiation for diagnostic or therapeutic purposes, survivors of the atomic bomb, and general populations exposed to different levels of background radiation. The last of these has not, so far, been particularly fruitful, partly because the very low risks would require enormous sample sizes and very careful control of confounding variables to demonstrate effects. Of the remaining, the occupationally exposed have the advantage of being the most representative of unselected populations, but the measurement of their exposures is generally the worst. The medical patients have much better dosimetry, but their risks may be affected by the diseases for which they received the radiation. The atomic bomb survivors are by far the largest group exposed to low doses, but they may represent a healthier subset of those exposed and problems with their dosimetry have recently been uncovered. The specific groups which are described in the next chapter are summarized in Table 4.1.

4.1.2.3 Measurement of exposure. For the purpose of this report, we have restricted attention to those studies which offer quantitative data on the degree of exposure. These have generally been measured either by biological assay of the retained dose or by a combination of environmental measurements and personal histories. For example, the exposures of the radium dial painters could not be estimated by the latter method because individual techniques appear to have been a major determinant of dose; instead, the quantity of radium retained was measured many years after the exposure and extrapolated backwards in time to estimate the applied dose (No55). On the other hand, in miners there is no practical bioassay of cumulative exposure to the short lived radon daughters because the half-lives are so short; instead, data on exposure has come from measurements (or estimates) of the concentrations of radon or its daughters at various locations and times in the mines, and from payroll records which indicate the amounts of times spent at these locations; these could then be combined to estimate individual- and time-specific cumulative exposure indices (e.g. Lu71). So far, no simple and reliable method of personal dosimetry for alpha radiation has been developed. The principles of environmental and biological dosimetry are described in Section 3.4.

4.1.2.4 Calculation of risk. As described in Section 4.1.1, the measurement of risk in a cohort study involves ascertainment of the deaths (or events under study) and a knowledge of the population at risk. If both are known, death rates can be calculated for each exposure subgroup. However, as rates for most diseases vary considerably with age, calendar year and other variables, valid comparison requires adjustment for these factors. This is usually done by the person-years method, in which age- and calendar year-specific death rates for a standard population are multiplied by the age- and year-specific person-years at risk in each exposure group to obtain expected deaths;

the ratio of total observed to total expected, known as the (indirect) standardized mortality ratio is an estimate of relative risk, and the difference between observed and expected divided by the total person-years estimates attributable risk. If the population at risk is not known, expected deaths for specific causes can be calculated using the age- and year-specific fractions of all deaths due to each cause (Ku78b) and relative risk can be estimated as above (the standardized proportional mortality ratio, SPMR) but attributable risk cannot be estimated. However, the SPMR can be misleading if the rates for other causes of death are also increased or decreased.

4.1.3 Criteria for Evaluating Studies

With this general framework in mind, we list below the particular criteria used to evaluate the studies described in the next chapter. A fuller discussion of these and other criteria is given in a review by Baumgarten and Oseasohn (Ba79).

Type of study. Is it a case-control, proportional mortality or true cohort study?

Representativeness of population. Are the conclusions from this study group generalizable to any population of interest?

Sample size. Given the number of subjects and length of follow-up, would sufficiently many excess deaths be anticipated for the numbers to be statistically significant?

Length of follow-up. Is it long in relation to the presumed latent period?

Choice of reference. Is an external standard used to calculate expected deaths and if so is it properly comparable (e.g. note the healthy worker effect, McM76)? If there is no proper external standard, is there a satisfactory internal control group?

Exposure measurements. Has the relevant factor been assessed (e.g. radon daughters rather than radon gas)? What proportion of the assessments were measured rather than estimated? How well would they reflect an individual's exposure? Have exposures in jobs outside the industry been taken into account?

Ascertainment of outcomes. Are deaths from all causes given or only the specific cause under study? Is any information given on the completeness of ascertainment or loss to follow-up? Is there any reason to suspect losses might be related to exposure, mortality, or confounding variables?

Statistical methods. Was an appropriate method of cohort analysis used? What index of cumulative exposure was used and how were changes in exposure status taken into account? What attempts were made to take latency into account?

Confounding and modifying factors. What factors were used for adjustment in the analysis? Are results presented separately for different levels of any modifying factors? What other factors were at least discussed? Are there any potentially important factors that were ignored?

Bias. What measures to minimize bias were used, such as blinding?

Results. Taking the possible limitations into consideration, which of the findings can we have reasonable confidence in and how consistent are they with those of other studies?

Summary. What appear to be the principal strengths and weaknesses of each study?

4.2 STATISTICAL METHODS

Four types of questions are discussed in subsequent chapters of this report:

1. Is there evidence to support or contradict the assumption that risks depend linearly on dose for high-LET radiation? If linearity is rejected, how great is the degree of curvilinearity?
2. What is our best estimate of risk and its probable variation at particular levels of exposure?
3. Do these risks vary as a function of temporal factors, exposure to other agents, and other modifiers?
4. What is the projected risk over an entire lifetime under various scenarios of exposure?

The first two questions are essentially variants on the issue of describing dose-response relationships and are discussed together in the next section. The fourth is discussed in Section 4.2.2. The third is the subject of Chapter 7, but requires no further methodological discussion here.

4.2.1 Analysis of dose-response relationships

The methods of analyzing shapes and magnitudes of dose-response relationships can be classified in two ways. The first issue is whether the fundamental comparisons are made between studies, plotting average risk against average exposure for each entire study, or within studies, plotting risk against exposure in more narrowly defined subgroups of one study at a time. The second issue is whether such relationships are analyzed by testing differences between high and low dose groups or by fitting specific mathematical models to the data points.

4.2.1.1 Methodologic limitations. Before describing these methods of analysis, we must point out some potential pitfalls in any form of dose-response analysis. Inferences on the shape of dose-response relationships are even more susceptible to confounding than are inferences on their overall slopes. Three methodological problems are particularly important, the choice of reference for computing expectations, the effect of errors of measurement, and the treatment of latency.

Inappropriate choice of reference can lead to biased conclusions about shape by shifting the entire relative risk curve upwards or downwards by a constant multiplicative factor. The risk indices RRI and ARI (Section 4.1.1) will then be affected more at low doses than at high doses, giving the illusion of curvilinearity when in fact only the intercept and slope have been changed (Figure 4.2). A remedy to this problem is to estimate the intercept as well as slope and curvilinearity parameters, rather than anchoring the intercept at zero excess risk, but in our experience this frequently leads to quite unacceptable estimates or even failure to reach a solution at all.

This problem with estimating the intercept probably arises from errors in the measurement of exposure. These can be systematic or random, and either can bias fitted relationships (Co77b). Random error, for example, will tend to cause slopes to be underestimated and intercepts to be overestimated (Figure 4.3a), unless the intercept is constrained to its true value; the true value is of course unknown for the reasons given in the previous paragraph, but for practical purposes, constraining it to zero excess risk will tend to overcome the problem. In a similar way, attempts to fit power function relationships will also be biased by random error: here the exponent will tend to be underestimated and the coefficient overestimated (Figure 4.3b), unless the coefficient is constrained to its true value (which is certainly unknown).

Inadequate analysis of latency or too short a period of follow-up can similarly lead to biased conclusions about shape. For example, if latent periods are inversely related to dose, risks in the lower groups are more likely to be underestimated than in the higher groups, thus introducing a concave tendency to the data (Figure 4.4). Similar biases can occur even if latent periods are independent of dose, but "wasted doses" (those accumulated during the latent period preceding death) are not eliminated in exposure calculations and the fraction they contribute varies with exposure, for example if high exposures are associated with long periods of follow-up. There is no simple remedy to these problems without access to the original data to reanalyze latent period effects.

These issues are explored further in Section 8.1 and Appendix M. As statistical methods used in reporting risks vary considerably between studies, we have attempted to adjust these estimates in various ways in order to standardize comparisons between studies. For example, for the Newfoundland miners and Hiroshima survivors, we have used the lowest exposure group rather than national rates to calculate expected deaths because we feel the former provide a more meaningful intercept. Similarly, for the Czechoslovakian and Ontario uranium miners, we have eliminated the estimated deaths in the first ten years in an attempt to take latency into account; this same exclusion is explicitly made by the investigators in other studies. The details of these and other adjustments are provided in Appendix K.

4.2.1.2 Between- versus within-study comparisons. For certain sites, notably lung cancer, several studies provide estimates of risk which span quite different ranges of exposure. As these studies report different estimates of risk per unit dose, it is obviously of interest to see if there is any systematic pattern, and an obvious characteristic is the dose itself. For example, a plot of average risk of lung cancer per unit dose against average dose is provided in Figure 5.1. While such comparisons are useful for suggesting explanations for differences in risk, we feel they do not provide convincing evidence on dose-response for reasons of both validity and efficiency. From the point of view of validity, the studies may differ in the nature of the populations, the occupational setting, and methods of study, (e.g. the accuracy of dosimetry, length of follow-up, completeness of disease ascertainment, and statistical methods). Such differences might well be related to both exposure and disease in a way which could explain the observed pattern; this has frequently been observed by epidemiologists in other settings (Fr74). From the point of view of efficiency, any comparison of means must necessarily have very little statistical power because the exposures span a very wide range within each study and there is considerable overlap between studies.

For these reasons, we feel that only comparisons within studies can hope to offer unconfounded estimates of dose-response curves. However, as individual studies are smaller, particularly in certain exposure ranges, the precision of the estimates is reduced and several models may fit equally well. In an attempt to get around this problem, we have made comparisons within studies but have pooled these comparisons across studies in a manner which is statistically valid and avoids both the problems of confounding in between-study comparisons and of small numbers in within-study comparisons. These methods of pooled internal comparisons are described below.

4.2.1.3 Subgroup comparisons versus model fitting. Our basic objective is to provide risk estimates for particular exposure levels for the purpose of setting standards. Such estimates can only come from fitting dose-response models, as no epidemiological study could hope to provide a direct estimate of risk on a sufficiently large group of people exposed to the same level. Other advantages of the modelling approach are (1) that it makes use of all the data rather than just the subgroup of interest and is therefore much more precise, (2) that it avoids the problem of choosing arbitrary subgroups, which must be neither so large as to conceal a substantial range of risks nor so small as to produce imprecise estimates of risk, (3) that it provides the statistically most powerful test of curvilinearity, and (4) that it offers some basis for extrapolation to lower doses than are actually observed in the studies. The method of model fitting using weighted least squares is described in Appendix J. The specific models considered are special cases of the general forms:

$$AR_{ij} = (a_i^* + b_i^* D_{ij}^{c_i})\ 0.5^{D_{ij}/d_i} \qquad [4.1]$$

$$RR_{ij} = (a_i + b_i D_{ij}^{c_i})\ 0.5^{D_{ij}/d_i} \qquad [4.2]$$

where AR is the attributable rate (observed minus expected divided by person-years), RR is the relative risk (observed divided by expected), D is exposure in WLM, and A^*, a, b^*, b, c, and d are parameters ("regression coefficients") to be estimated from the data; the subscripts denote the jth subgroup of study i. This model is a combination of two popular models, the "cell killing" model widely used in radiobiology, characterized by the constraint $c = 1$ (BEIR80, UN77), and the "nonlinear" model proposed by Morgan (Mo78) and others, characterized by $d=\infty$, for which the rationale is provided in Section 2.4. Both can show convex behaviour, the essential difference between them being that the cell killing model is linear at low doses, with curvature becoming apparent only at doses of over about 1000 WLM, whereas the nonlinear model is most strongly curvilinear at low doses. For various purposes, we consider special cases of the general model by applying various constraints. Thus, for example, except to allow for the methodologic limitations discussed in Section 4.2.1.1, we have constrained $a_i^*=0$ and $a_i=1$ for most analyses. Similarly, the method of pooled internal comparisons is obtained by constraining $c_i=c$ and $d_i=d$ while allowing the b_i to vary between studies. For purposes of describing curvilinearity, we have restricted our analyses to model [4.2] because model [4.1] can be derived from it merely by multiplying by the expected death rates; thus, unless these vary considerably between exposure groups, inferences about the curvilinearity parameters c and d are unlikely to be affected. The calculations were carried out on McGill University's AMDAHL V7 computer using the Statistical Analysis System (SAS79) procedure NLIN, which provides estimates of the parameters and their standard errors as well as chi-square tests of goodness-of-fit. The raw data used for fitting is reproduced in Appendix K.

We recognize that model fitting can lead to incorrect conclusions if the model does not adequately describe the data or if too extreme an extrapolation is done. To guard against this we have visually inspected the data to see if some other model might be suggested, and have reported direct risk estimates for various exposure subgroups. We have also repeated the model fitting procedure excluding the subgroups with very high exposure (at various arbitrary levels).

4.2.2 Life table projection of risk estimates

The model fitting procedure provides an estimate of excess risk at any dose level which is valid for the ages and calendar years actually studied. To predict the eventual number of deaths from a specific cause in a population followed for an entire lifetime, we must make a further assumption about how these excess risks vary with age and year. For want of any data about mortality rates in the future, we have assumed today's rates and treated radiation effects as invariant over time; the error in these assumptions is unlikely to be very substantial. On the other hand, it is certainly probable that radiation effects are not constant with age. The most likely pattern is illustrated in Figure 4.5(a), in which there is no increase in risk for some time after first exposure, followed by an increase which starts during the latent period, possibly tapering off long after cessation of exposure. Unfortunately, quantitative data on the latent period for radiation effects is presently very limited, so this model is not very reliable for life table risk projection. Most presently available data leave us with little alternative but to assume that excess risks per unit dose continue either as a constant additional factor over all ages starting some years after first exposure (the attributable risk projection model, Figure 4.5(b)) or as a constant multiplicative factor (the relative risk projection model, Figure 4.5(c)). Either may under- or overestimate the ultimate risk, but in the absence of complete data covering the whole lifetime (currently unavailable) the relative risk projection model will generally exceed the other by a substantial factor (from three to ten fold); clearly with full data, both must agree. Where age-specific risk indices are available, the differences between the two projection models will be considerably reduced. An empirical comparison of the two models, based on computer simulation is provided in Appendix M. The observational support for the two models has recently been reviewed by Cohen (Co79), who concludes by rejecting the relative risk model. We, however, find his analysis seriously flawed and have a clear preference for the relative risk model. The data to support our position is described in the following three chapters.

Whichever projection model is assumed, the calculations involve aging a hypothetical population of 100,000 persons of age 15 through an actuarial life table, in which the death rates from the cause of interest at each age are increased by the value of the fitted dose-response function, where exposure is accumulated to that age (or to some fixed interval before it). The details of these calculations are provided in Appendix L.

TABLE 4.1

TYPES OF POPULATIONS USED TO STUDY RADIATION EFFECTS

Population	Advantages	Disadvantages
Occupationally Exposed	Representative of population for which standards are to be set	Poor dosimetry
Medical patients	Good dosimetry	Risks may be affected by underlying diseases
Atomic bomb survivors	Very large sample size Many subjects at low doses	Possible survival of the fittest Possible problems with dosimetry Poor ascertainment for some causes of death
General populations	Potential to demonstrate effects of very low levels of radiation	Very small effects expected Difficulty of controlling confounding factors

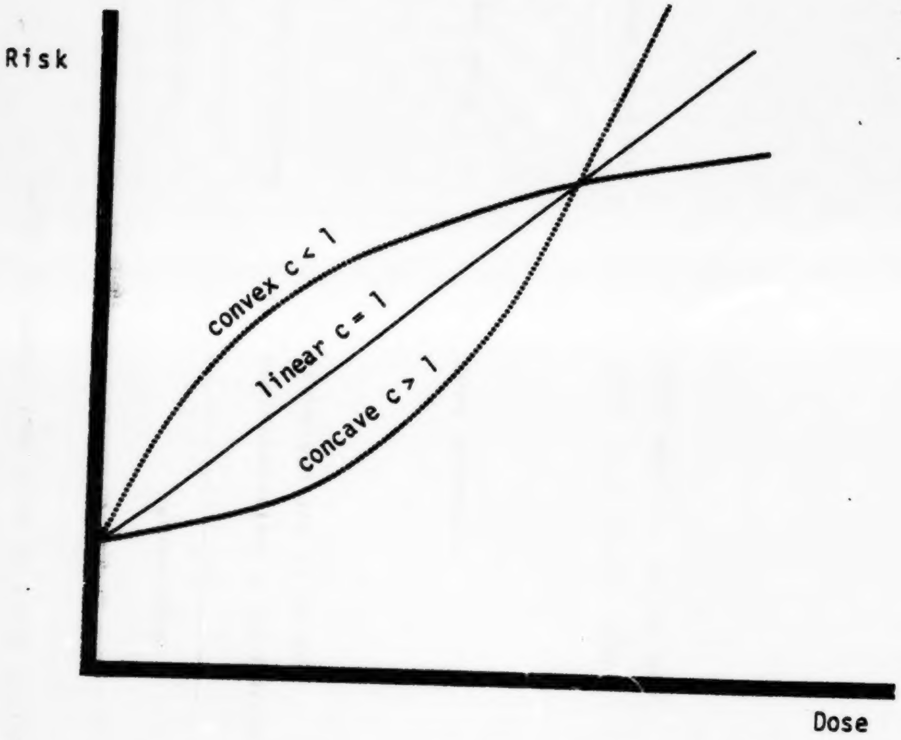


FIGURE 4.1

HYPOTHETICAL TYPES OF DOSE-RESPONSE RELATIONS

GENERAL FORM, $R = a + bD^c$

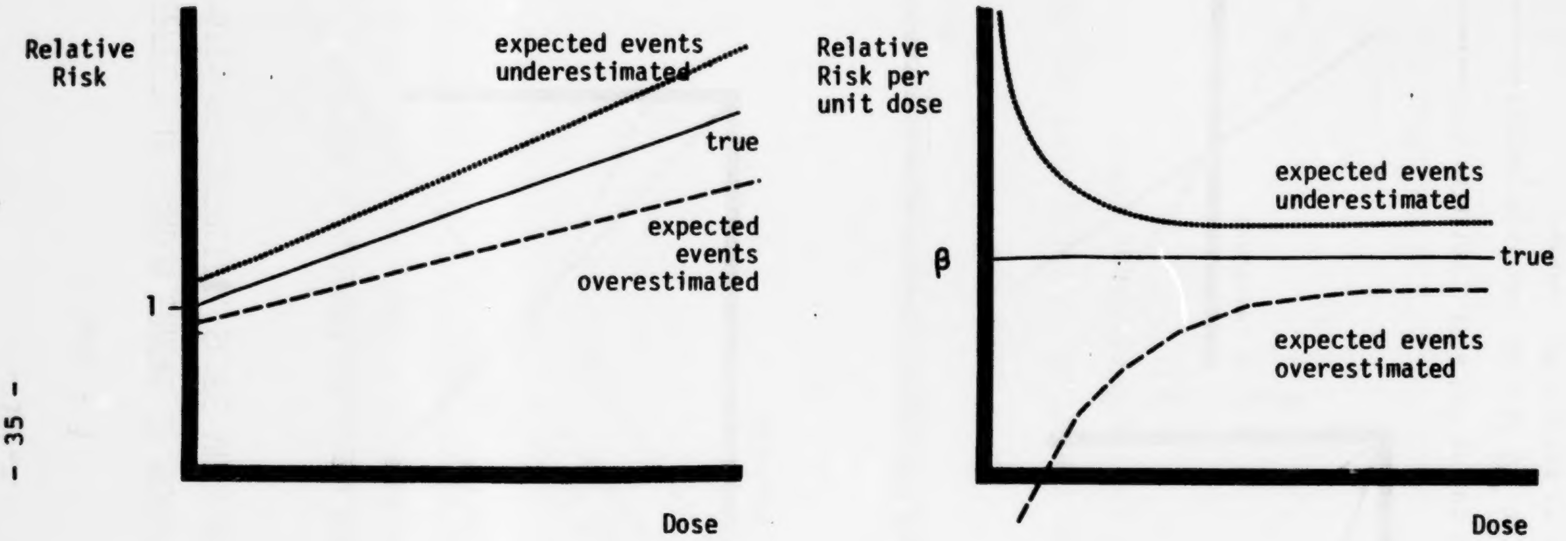


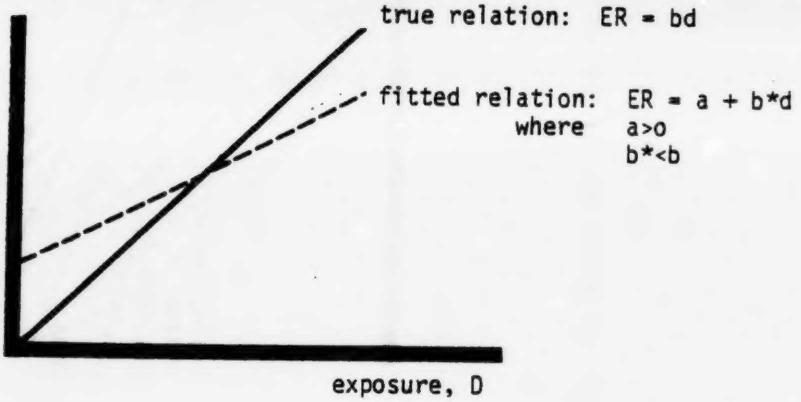
FIGURE 4.2

EFFECT OF ERRORS IN CALCULATING EXPECTED EVENTS ON DOSE-RESPONSE RELATIONS

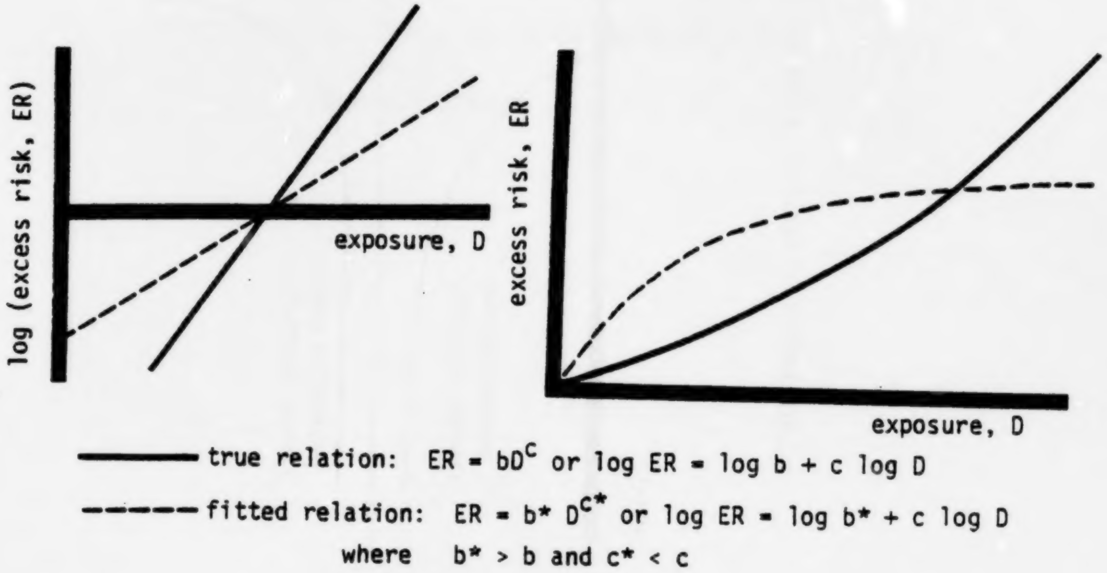
FIGURE 4.3

EFFECTS OF RANDOM ERRORS OF MEASUREMENT ON ESTIMATES OF INTERCEPT, SLOPE AND CURVILINIARITY

Effect on intercept and slope, exponent constrained to unity


true relation: $ER = bd$
fitted relation: $ER = a + b^*d$
where $a>o$
$b^*<b$
exposure, D

Effect on slope and exponent, intercept constrained to zero


log (excess risk, ER)
exposure, D
excess risk, ER
exposure, D
true relation: $ER = bD^c$ or $\log ER = \log b + c \log D$
fitted relation: $ER = b^* D^{c^*}$ or $\log ER = \log b^* + c \log D$
where $b^* > b$ and $c^* < c$

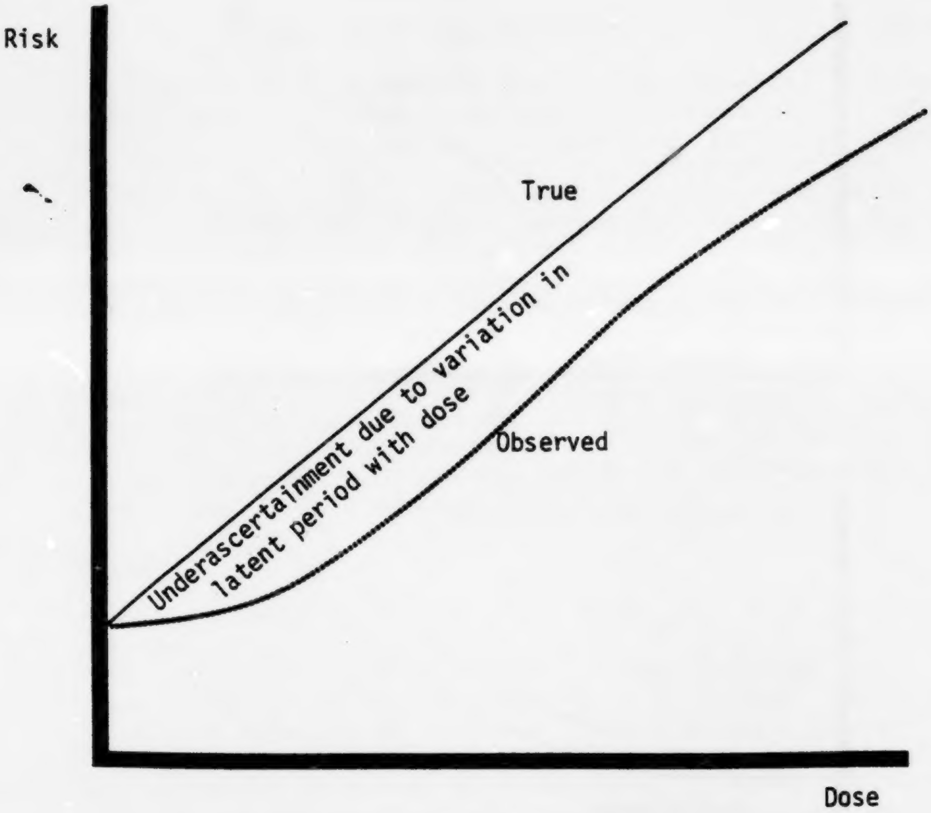


FIGURE 4.4

EFFECT OF VARIATION IN THE LATENT PERIOD ON THE DOSE-RESPONSE CURVE

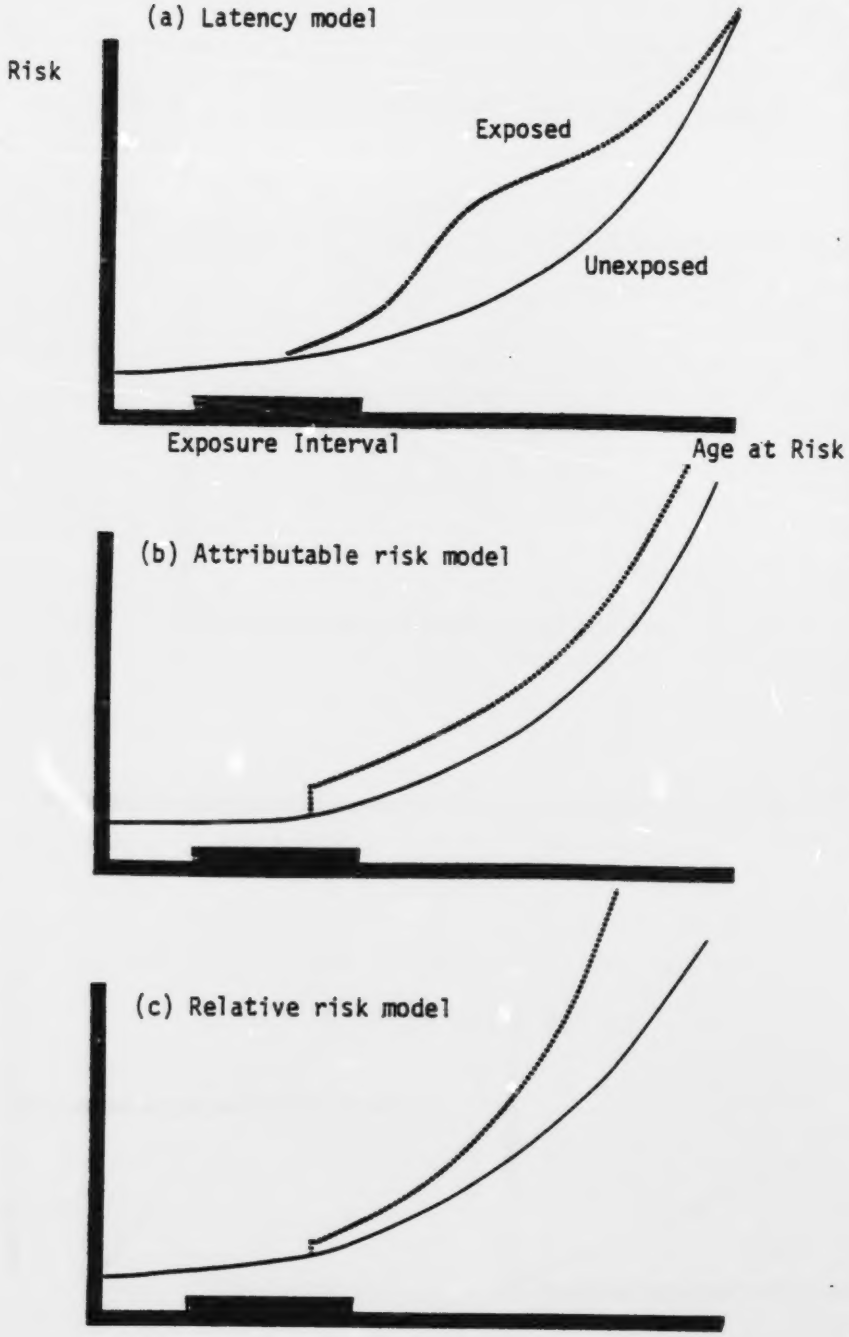

(a) Latency model
Risk
Exposed
Unexposed
Exposure Interval
Age at Risk
(b) Attributable risk model
(c) Relative risk model

FIGURE 4.5

THREE MODELS FOR PROJECTING RISK ESTIMATES
BEYOND THE END OF FOLLOW-UP

CHAPTER 5

EPIDEMIOLOGICAL EVIDENCE

This chapter provides a summary of the epidemiological evidence on the forms and slopes of dose-response relationships for alpha radiation on a site-by-site basis. Statements in this chapter are intended only as averages over entire populations. A discussion of the major factors which might require estimates to be higher or lower in particular subpopulations follows in chapter 7, based on both human and animal data. In the interest of brevity, only the major findings are reported here. The reader is referred to Appendix I for more detailed critiques of the methodology of each study and to Appendix K for explanations of the particular choices of data selected and any adjustments made to express these data in a form comparable to that used in reporting findings from the Colorado study. A summary of the major studies used for risk estimation, their strengths and limitations, and the main conclusions on forms of dose-response relations is provided in the final Table 5.10.

5.1 LUNG CANCER

The lung is the primary site at risk from exposure to radon daughters and may also be a major site at risk from other internal alpha emitters, particularly those inhaled such as plutonium from fallout or other sources. The most important sources of data are studies of various mining groups exposed to radon daughters. So far, no human studies provide adequate data for estimating risks of lung cancer from other internal emitters, though the largely negative studies of lung cancers in persons exposed to plutonium, thorium and radium are discussed in Appendix I.2.

Five mining populations have been reported in sufficient detail to allow internal comparisons of dose-response relationships. These are summarized in Table 5.1 and Figure 5.1 (solid circles) and are discussed below and in more detail in Appendix I.1. In addition, several other mining populations have been described, the data from which allow at least a single estimate to be made of average risk in relation to average dose. These are included in Table 5.1 and Figure 5.1 (open circles) to summarize the range of average effects but are not used in drawing any inferences about shapes of relationships because of the strong likelihood of confounding when making comparisons between populations (see Section 4.2.1.2). For completeness, Appendix I.2 mentions a few studies which fail to provide adequate descriptions of either risk or dose or both.

5.1.1 The major studies

5.1.1.1 Czechoslovakian uranium miners. This is a cohort of about 2200 uranium miners hired between 1948 and 1952 who were exposed to moderately high levels of radon daughters (mean cumulative exposure about 300 WLM) and followed to the end of 1973 (Se76a, Ku78a) or 1975 (Ku79). (An additional cohort hired between 1953 and 1957 is not included in the results reported here.)

The principal strengths of this study are the quantity of exposure data available (though the measurements are of radon gas rather than of its daughters), the number of workers exposed to moderately low doses, and the relatively long period of follow-up (mean 26 years). Its main limitation is the inappropriateness of the methods of statistical analysis (see Appendices I and K).

For the entire cohort, a lung cancer rate of 3720 per 10^6 PY was observed, compared with 750 per 10^6 PY expected. This leads to an average attributable risk of 16.82 ± 1.40 per 10^6 PY-WLM and an excess relative risk of 1.92 ± 0.16 per 10^2 WLM, (Table 5.1). These estimates include an adjustment (Appendix K) based on the assumption that no excess cancers would have occurred in the first ten years of employment. Depending on the method of analysis used by the authors in different papers, the dose relation appears either slightly convex or slightly concave, but the departure from linearity is small by either method (Table 5.2 and Figure 5.2).

5.1.1.2 Colorado plateau uranium miners. This is a cohort study of 3356 white and 780 non-white uranium miners and millers in the Colorado Plateau (a four-state area) who had worked for at least one month underground before January 1964 and who had been followed through September 1974 (Ar76, Ar78a, BEIR80).

This is a large, well traced, and well analyzed study of a group of miners exposed to high levels of radiation. It is also the only study in which data on both smoking and radon daughters are available on the same individuals. Its principle limitations are the poor quality of the exposure data and the small numbers exposed to low levels.

For the entire cohort, 159 lung cancer deaths have been observed in the period starting 10 years after the first exposure, compared with 25.24 expected, leading to an average attributable risk of 3.52 ± 0.33 per 10^6 PY-WLM or an excess relative risk of 0.45 ± 0.04 per 10^2 WLM (Table 5.1). Of all the mining populations described, these estimates are by far the lowest. Excess cancers are apparent in all categories beyond 120 WLM, but the slope decreases strongly with increasing dose (Figure 5.3), ranging from RRI = 0.92 under 600 WLM to 0.39 over 600 WLM, a ratio of 2.4 (Table 5.2). However like the Czechoslovakia data, this increase in slope with decreasing exposure does not continue into the lowest exposure category.

5.1.1.3 Ontario uranium miners. In a cohort of about 10,000 miners who had first worked in the Ontario uranium mines between

1954 and 1963, 81 fatal lung cancers occurring before the end of 1974 have been ascertained (Ha76). However both the shortfall of deaths from other causes (including such causes as respiratory disease frequently found among miners) and additional pre-1974 cancers uncovered by the on-going tracing of the cohort suggest that lung cancer may have been under-ascertained by 50% or more.

The greatest merit of this study is the very large number of men exposed for short periods and thus getting low doses (mean cumulative exposure 36 WLM). As time progresses, this study will become an increasingly important source of data on the adequacy of present standards. At present, its principal limitations are the shortness of the follow-up period, the probable underascertainment, the quality of the exposure information, and the failure to take age, year, smoking, other exposures, or any other confounders into account. An additional potential cause of error is that the Ontario mines have significant amounts of thoron present. As the WLM would have been measured on the assumption that only radon were present, the actual dose may be underestimated by about 30-50% - (see Appendix E).

For the entire cohort, 45.1 lung cancer deaths would have been expected over the period of observation. As 19 of the 81 observed deaths occurred within ten years of first employment, we have subtracted these from both observed and expected to account for latency in a fashion similar to that used in the other studies. This leads to an attributable risk of 9.59 ± 2.07 per 10^6 PY-WLM or an excess relative risk of 3.97 ± 0.86 per 10^2 WLM (Table 5.1). Dose-response is based on a comparison of the lung cancer cases with an equal number of controls sampled from the survivors (He76). The results show a clear excess in risk above 60 WLM with a suggestion of concavity (Table 5.2 and Figure 5.2). The curvilinearity may, however, be an artefact of either shorter latency or better ascertainment at higher doses.

5.1.1.4 Newfoundland fluorspar miners. Preliminary findings have been reported from a cohort study of 2414 males who had ever worked for a month or more in any capacity for the fluorspar (calcium fluoride) mines of Newfoundland between 1933 and 1971 (dV80). Although fluorspar is not itself radioactive, radon gas entered the mines dissolved in water flowing through them and produced fairly high working levels (mean cumulative exposure 204 WLM). These workers have been followed through 1971, for an average of 20 years of observation.

These data have several important limitations, notably the quality of the exposure data, the lack of a suitable basis for estimating expected deaths, and the failure to take latency into account. Information on smoking and on the trace rate would also be desirable (but this is also true of most of the other studies).

Seventy-one lung cancer deaths were observed, 65 of them among underground miners. Because of the unusually high prevalence of smoking among this cohort, use of Newfoundland death rates artificially exaggerates the excess attributable to radiation and would make dose-response analysis impossible. Instead, the entire cohort has been used as the standard, and the rates scaled so that expected deaths equal those observed among the surface workers (dV80). On this basis, the excess relative risk is 2.30 ± 0.34 per 10^2 WLM (Table 5.1), with some suggestion of concavity (RRI = 1.73 for 1-479 WLM vs. 2.83 for 480+ WLM, Table 5.2 and Figure 5.2). However, these findings must be considered cautiously because of the doubtfulness of the expected rates and the failure to take account of latency (Section 4.2.1).

5.1.1.5 Swedish metal miners. Mortality has been described in three mining areas of Sweden (Table 5.1), Kiruna (Jo73), Zinkgruven (Ax78), and Malmberget (Re74) but none of these provide breakdowns of risk by exposure. However, one preliminary report of a national survey (Sn74) describes 36 lung cancers compared with 6.07 expected, producing an attributable risk of 3.43 ± 0.69 per 10^6 of PY-WLM or an excess relative risk of 3.03 ± 0.61 per 10^2 WLM (Table 5.1). A comparison of exposure groups shows a considerable decrease in slope with increasing exposure (RRI = 4.24 per 10^2 WLM in the two lowest groups vs. 2.84 in the two highest (Table 5.2 and Figure 5.2). However, as the ranges of exposure overlap it is likely the groups may represent entire mines rather than individuals, and thus the comparison may be subject to confounding; only a very limited description of the epidemiologic methods used has so far been published.

5.1.1.6 Atomic bomb survivors. By far the largest population for study of the effects of a wide range of doses of radiation (from low to near lethal) is the cohort of 82,000 survivors of the atomic bombs at Hiroshima and Nagasaki, traced from 1950 to 1974 (Be78a). Because of the differences in the construction of the two bombs, the two cohorts may have received different qualities of radiation: the Nagasaki dose consisted almost entirely of gamma radiation whereas the Hiroshima dose was thought to have included a substantial neutron dose. In this section, we summarize our findings in terms of a "dose equivalent" (DE, in rems, Appendix K.2.6) based on the only kerma dose estimates (T65) available at the time of writing (Be78a), combined with estimates of the ratio of absorbed to kerma doses (Ke79) and an assumed quality factor of 10 for neutrons. We had also attempted to separate the two components using weighted least squares (as had been reported for leukemia in BEIR80, see Section 5.4.1.6), but have not included these results in this report because of the recent discovery of serious errors in the assessments of the relative strength of the two components.

The principal merits of these data are their very large size, particularly at low doses, and the completeness of the tracing. However they have a number of serious limitations (discussed more fully in Appendix I): (1) the difficulty of unscrambling neutron and gamma effects, (2) the dubious relevance of neutron effects to conclusions about alpha radiation, (3) the possibility of a dose related "survival of the fittest" effect, as those with the largest dose will also have received most blast trauma, (4) the inaccuracy of the death certification of lung cancer (and perhaps other causes), (5) the possible difference between the effects of this very short high dose-rate exposure and the long-term low dose-rate exposure of miners, (6) social or racial differences which have resulted in very low population rates for lung cancer in Japan (Se69), and (7) doubts (which have become greatly increased in recent months (Lo80)) about the validity of T65 dosimetry. For these reasons, we have not included the atom bomb survivors with the five mining populations in the synthesis which follows, except to provide an upper limit to curvilinearity.

Using the zero-dose group as the reference, 152 lung cancers were observed at Hiroshima compared with 109.50 expected and 57 observed at Nagasaki compared with 46.46 expected. These lead to estimates of attributable risk of 1.74 ± 0.50 and 0.84 ± 0.61 per 10^6 PY-rem (DE) respectively and of excess relative risk of 1.02 ± 0.30 and 0.56 ± 0.41 per 10^2 rem respectively (Table 5.1). There is a dose-relation at both cities, though it is clear at Nagasaki only after considerable regrouping, and the slope there is only half that at Hiroshima (Figure 5.2). The Hiroshima data show greater convexity than any other study (RRI = 1.96 per 10^2 rem for 1-99 rads kerma, versus 0.45 for 100+ rads, Table 5.2). The Nagasaki data are too few for reliable inferences on curvature, but suggest slight concavity.

5.1.2 Synthesis of risk estimates

Having considered the qualitative appearance of the dose-response curves for each study separately, we now describe our efforts to fit specific mathematical models to the six studies (Figure 5.2) and in particular to combine the data to obtain best estimates of slope and curvilinearity. This analysis was motivated by a synthesis of summary data from all these studies by Archer, Radford and Alexson (Ar78b), who concluded that risks per unit dose decrease considerably with increasing dose. We find their analysis flawed in a number of ways, but a plot of our revised summary data (Figure 5.1) quite clearly suggest the same conclusion. Accepting all the limitations of such between-study comparisons (see Section 4.2.1.2), we have tried to reconcile this marked convexity of between-study comparisons with the smaller convexity or even concavity of the within-study comparisons discussed earlier.

Before attempting to combine the studies, we first examined the fit of the general model [4.2] described in Section 4.2.1.3 to each study separately. Table 5.3 gives the parameter estimates, their standard errors, and the goodness of fit statistics for each study fitted to each of three models, the linear (parameter b only), low-dose nonlinear (parameters b and c) and cell-killing (parameters b and d). None of the models would be significantly rejected and only the Colorado, Newfoundland, and Hiroshima studies provide even suggestive evidence of lack of fit to linearity. However, statistical power is greatly increased by testing the improvement in fit resulting from the addition of additional parameters to the linear model. Thus, though the fit of the linear model to the Colorado model is not significantly rejected, it is significantly improved by adding either an exponent ($\chi_1^2 = 8.48 - 1.84 = 6.64$, $p<0.01$). or a cell-killing term ($\chi_1{}^2 = 8.48 - 4.52 = 3.96$, $p<0.05$). Similarly, the fit to the Hiroshima data is significantly improved by adding an exponent ($\chi_1^2=6.38-0.25=6.17$, $p=0.013$), and almost significantly improved by adding a cell killing term ($\chi_1^2=6.38-2.71=3.67$, $p=0.055$). Substantial improvement is also obtained for the Czechoslovakia and Newfoundland data, but none of these are significant ($p>0.10$ for all). The estimates of c are completely consistent with the impression of each study given in Table 5.2. Thus, the Colorado, Czechoslovakia, Sweden and Hiroshima data suggest convexity ($c<1$) while the Newfoundland and Ontario data suggest concavity ($c>1$). For all four studies showing convexity, the non-linear model fit better than the cell killing models, though the differences in fit were trivial for Czechoslovakia and Ontario. Allowing the intercept, a, to be free led to divergence for Newfoundland, no improvement in fit for Hiroshima and Nagasaki (where the baseline was determined by the very large zero-rad group), and unacceptably large estimates for Colorado, Czechoslovakia, and Sweden. In no cases were we able to estimate the intercept, a, and either of the curvilinearity parameters, c or d, simultaneously.

Next we tried combining the studies in various ways. Because of the many possible differences between studies, we began by estimating a separate slope parameter b_i in each study while constraining the exponent and cell-killing terms to common values (cf. Section 4.2.1.3). In this way, we hoped to get the greatest possible power for detecting nonlinearity while avoiding the confounding effect of between-study differences in slope. For reasons given above (Sections 5.1.1.6) we excluded the Hiroshima data from this analysis. The results are given in the top part of Table 5.4. All of the models fit well, but the addition of a cell-killing term provides a significant improvement ($\chi_1^2 = 23.46 - 19.54 = 3.92$, $p<0.05$). The estimated exponent $\hat{c} = 0.92$, while suggesting convexity, is not significantly different from unity. The estimated slopes for each of these models are given in Table 5.5.

As we had particular doubts about the validity of dose-response inferences based on the Newfoundland and Ontario data, both of which suggested concavity (see above, Sections 5.1.1.3 and 5.1.1.4), we next tried to establish an upper limit to the convexity parameters. For this analysis, we included the Hiroshima data and excluded the Newfoundland and Ontario studies and the highest exposure category in the Colorado data. Even with these choices, the fit of the linear model is still good, but the improvement by adding either an exponent or a cell-killing term is now highly significant ($p<0.005$). The nonlinear model now fits slightly, but not significantly, better than the cell-killing model. Our most extreme estimate of curvilinearity is thus provided by an exponent $\hat{c} = 0.72$ (Table 5.4).

Finally, we tried fitting the general model to the five mining studies assuming a common slope. The reasons for doing this were to see if we could explain the marked curvilinearity apparent in Figure 5.1 by a common model and to obtain a "best" estimate of the parameters to recommend for setting standards. When all five populations were included, the resulting model was overwhelmingly rejected ($\chi^2_{23} = 128.4$). However, when the data points above 300 WLM were eliminated, the fit was considerably improved ($\chi^2_{13} = 28.94$). Considering the differences between studies it is hardly surprising that the lack of fit would still be significant, but the resulting estimate of a common slope (2.10 ± 0.25 per 10^2 WLM) is probably a reasonable average value. However, because the exposure range has been so narrowly restricted, any opportunity to demonstrate significant curvilinearity has been lost.

Of the five mining groups, the Colorado data is clearly the outlier responsible for most of the lack of fit to a common slope model. At least part of the explanation for the very low slope estimate in the Colorado study may be the systematic overestimation of exposures there, as discussed in Section 3.4.4.5. For this reason, and because we wanted an "upper limit to the best estimate" of slope, we made an analysis excluding the Colorado data. The lack of fit to the three models was now only marginally significant and the differences between the models trivial. The resulting slope estimates are given in the bottom section of Table 5.5. We have chosen the value 2.28 ± 0.35 per 10^2 WLM from the cell-killing model as our best estimate of excess relative risk at low doses in the extrapolations and projections provided in Chapter 8, but these can be proportionally scaled upward or downward for different choices of slope, if desired. These estimates of common slope can be thought of as weighted averages of the separate slopes for each study, where the weights are roughly proportional to the number of excess deaths. Thus, by far the heaviest weight is given to the estimates based on the Czechoslovakia data, and the common slope estimates are therefore only slightly larger than the Czechoslovakia estimates. The inverse of the slope estimates can be given the interpretation of a "doubling dose", that is, the dose at which the lung cancer risk is doubled: for the cell killing model, our best estimate of the doubling dose is therefore 44 WLM, compared with 39 WLM ($= [1/0.0306]^{1/0.952}$) under the nonlinear model, or 45 WLM under the linear model.

Table 5.6 provides a description of the magnitude of the differences between the various models at different levels of cumulative exposure. If the comparison is made in relative terms (i.e. ratios of excess risks), then the differences between models are most pronounced at low doses, and the nonlinear model differs from the linear model much more than does the cell killing model. However, as the risks predicted by all models are small at low doses, the absolute differences are small at low doses, becoming more important at high doses. All differences between models are reduced when the fits are based on the combined data, and reduced further under the common slope constraint. However, even the largest of the discrepancies between predicted risks do not vary by more than a factor of two.

5.1.3 Comparison with other risk estimates

Most other risk estimates are not directly comparable with our figure of 2.28 per 10^2WLM because they are expressed in attributable rather than excess relative risk terms. UN77 gives a range of 200 to 450 per 10^6 person-WLM over a 40-year effect period, which, assuming a 10-year minimum latent period, translates to 6.7 to 15 per 10^6 PY-WLM. BEIR80 suggests a risk of 10 per 10^6PY-WLM over the age-at-risk range 35 to 49, 20 per 10^6PY-WLM over age 50 to 64, and 50 per 10^6PY-WLM over age 65; these estimates are thus higher than the UN77 range unless one makes an additional assumption (not suggested in BEIR80) that the effect period does not span the entire lifetime (see Section 8.2.1.2 for calculations of the effect of making this assumption). Archer et al. (Ar78b) have fitted an exponential relationship to a set of attributable risk indices similar to those given in Table 5.1 to arrive at an estimate of ARI = 33.5 exp(-0.0016D), which equals 28.5 per 10^6Py-WLM at 100 WLM, comparable to the BEIR80 estimate. Finally, Evans et al. (Ev81) have recommended as an upper limit for the general population a figure of 100 per 10^6PY-WLM, which incorporates a two to three-fold adjustment for lower breathing rates; their estimate, scaled back up for miners, is thus comparable with the lower end of the UN77 range.

These various estimates therefore span the range of ARIs quoted in Table 5.1. Exact comparison with our RRI estimate requires the life table calculations provided in Section 8.2.1.2. However, a rough comparison is possible by multiplying our estimate of 2.28 per 10^2PY by the crude death rate for Canadian males over 25 years of age of 10.2 per 10^4PY to arrive at a rough attributable risk estimate of 23.3 per 10^6PY-WLM, well within the range quoted above. Corresponding calculations for the three groups give estimates of 3.9 (age 35-49), 32.7 (50-64), and 90.2 (65+) per 10^6PY-WLM, similar on average to the BEIR80 figures but varying more rapidly with age.

5.2 BONE SARCOMA

Bone sarcoma is the most important adverse effect associated with exposure to radium and is likely also to be the primary concern for those other radionuclides which, when taken internally, are deposited in the bone because of their chemical similarity to calcium (though evidence for those others at present comes only from animal studies). Epidemiological evidence on bone sarcomas comes mainly from studies of luminous dial painters and patients receiving radium injections. In addition, a mixed bag of subjects including dial painters, patients, chemists and others was assembled at M.I.T. and is continuing to be expanded now at the Center for Human Radiobiology of Argonne National Laboratory. These studies have also described carcinomas of the nasal sinuses and other somatic effects, reviewed in Sections 5.3 and 5.4. Finally, limited data on bone sarcomas have recently become available on thorotrast patients.

5.2.1 Luminous dial painters

A cohort of 1474 women employed in the U.S. radium-dial painting industry before 1930 has been identified and traced through 1976 (Ro78a). They had ingested ^{226}Ra (half life 1600 years) and ^{228}Ra (half life 5.75 years) through their practice of licking the paint brushes to obtain a fine point. About half of the cohort traced have had radium body burdens determined; these could be extrapolated backwards in time to estimate system intake (measured in units of microcuries, μCi).

The principal strengths of this study are its very long period of observation and the fact that bone sarcoma is so rare that probably all of the sarcomas can be presumed to have been radiation induced, and confounding factors can therefore be ignored. Its main limitation is that only about half of those exposed were measured and there are several reasons to suspect that these may be unrepresentative of the total cohort in terms of either exposure or disease or both (see Appendix I). In addition, the dosimetry is less reliable than in the radium patients described below.

Bone sarcomas have been discovered in 38 of the 759 women with measured body burdens. The data are shown in Figure 5.3, relating the systemic intake to the death rate in person-years at risk, assuming a five year minimum latent period. Excluding those with less than 0.5 μCi exposure (whose measurements were in doubt and who anyway had little influence on dose-response fitting (Ro78a)), we have fitted the remaining seven groups to the general form $R = bD^c 0.5^{D/d}$ where R is the sarcoma rate per person-years of risk (PY) and D is systemic intake (in μCi). The resulting fits are described in the top part of Table 5.7 and in Figure 5.3. With c constrained to unity, there was a suggestion of lack of fit ($p<0.10$) and allowing c to be free improved the fit significantly ($\hat{c} = 2.21$, $\chi_1^2 = 8.61$, $p = .003$). However, it must be borne in mind that this strong degree of concavity could be either a true nonlinearity in the dose-response relation or an artifact of a dose-related tracing bias. Nevertheless, the original authors found that exclusion of the exhumed cases had a minimal effect on their fitted relations.

5.2.2 German radium injections

A cohort of 204 juvenile and 612 adult patients, who had been injected with $^{224}\mathrm{Ra}$ (half-life 3.62 days) for treatment of bone tuberculosis, ankylosing spondylitis and other diseases between 1944 and 1951 (Sp70), has now been traced through June 1974 (Sp78, Ma78). The patients were identified through hospital and doctors' records of treatment rather than as a result of the appearance of bone sarcoma. Exposure was estimated in terms of average skeletal dose (in rads) from information about applied doses and age or body weight contained in the medical records.

Although the period of follow-up is very much shorter than for the dial painters, the bone sarcomas appear to have arisen much earlier, peaking at six to eight years after first injection, with only one new case occurring since the end of 1969. (This may be due to the much shorter half-life of the isotope, so that the dose was acute, in contrast to the chronic doses received by the dial painters). Thus the effect has probably been nearly completely expressed by now and follow-up appears to have been very good. Another strength of the study is the quality of the dose information and the opportunity to examine the potentially modifying effects of dose fractionation and age at injection. Like the other study, virtually all the sarcomas can be presumed to have been radiation induced. However, it is possible that either the underlying diseases or other drugs the patients received could have influenced the risk of sarcoma or the other effects described in Section 5.4; for a sampling of opinion on this important point, the reader is referred to the discussion following Sp78.

The data for juveniles and adults have been fitted to dose-response models separately as described in Table 5.7 and Figure 5.3. Here, R is given in units of cumulative incidence (sarcomas divided by subjects at risk, rather than person-years at risk), D is given in units of average skeletal dose (in rads), and a complementary exponential transformation is used to convert rates to risks as described in Section 6.1.5. While both sets show some concavity ($\hat{c}$ = 2.25 and 1.25 respectively), for neither is the departure from linearity significant, even when pooled ($\hat{c}$ = 1.55, χ_1^2 = 1.48, p=0.22) despite a sample size comparable to that of the dial painters. The difference in results may be due to true differences in the biological effects of the isotopes or to chance variation, but it would also be consistent with a truly linear relationship, which was distorted in the dial painters by a dose-related ascertainment bias.

5.2.3 The MIT-CHR Series

Two independent series of persons exposed to radium have been studied at the Massachusetts Institute of Technology (Ev74) and the Argonne National Laboratory (Fi69b). Around 1970, these two series were combined and further studies of radium-exposed subjects centralized under the Center for Human Radiobiology (CHR). Names of 3803 individuals have been assembled, consisting of 2828 dial painters, 492 chemists and other laboratory workers, 383 patients who were injected with radium or drank radium solutions for "medicinal" purposes, and 100 persons exposed through miscellaneous routes (Ro78b). There may be some overlap between the dial painters in this group and those described above (Ro78a) but neither paper cross-references the other; it is also unclear whether all the subjects in the MIT series (Ev74) are included in the CHR publication (Ro78b).

Both series include a substantial number of subjects (including more than half of the tumor cases) who were identified because of their symptoms; conversely fewer than half of the subjects identified on objective lists of exposed persons have been located and had their body burdens measured. This potentially invalidates both series (and, for that matter, perhaps also the dial painters described above) for studying either shapes or slopes of dose-response relations. In an effort to remedy the problem, both authors have subdivided their cases into those that were "epidemiologically suitable" and those not (Figure 5.3). However, as more than three quarters of the high dose (greater than 5000 rads) sarcomas are classified as unacceptable, the group which remains could also be unrepresentative. For example, in the MIT series, the acceptable subjects show a stronger cell killing effect ($\hat{d}$ = 5037 vs. 9342 μCi for all subjects, Table 5.7) reflecting the greater exclusions at high doses, but also show slightly greater concavity at low doses ($\hat{c}$ = 1.90 vs. 1.53). However though all series show some concavity, the departures from linearity are not significant for any, the greatest improvement in fit being the "suitable" MIT subjects ($\chi_1^2 = 3.63$, $p=0.057$).

5.2.4 Thorotrast patients

Fifteen bone sarcomas have been reported among patients injected with thorotrast, a colloidal suspension of thorium dioxide in dextrin used for diagnostic radiography (Ha79). Six of these (three histologically confirmed) have occurred among the three systematically traced populations (Denmark, Portugal and Germany) for which about 0.5 would have been expected to occur Based on a dose estimate of 1 rad/year to the marrow-free skeleton, a tentative risk estimate of 55 to 120 bone sarcomas/10^6 person-rad has been suggested, but this may need to be revised upwards in the light of the new cases reported in the addendum to Ha79.

5.2.5 Summary of risk estimates

In summary, we feel that only the female luminous dial painters and the German radium injection studies provide valid evidence on dose-response relations. both show some degree of concavity, though the effect is more marked for the dial painters. where it may be due in part to a dose-related tracing bias. Hence, our risk estimates are more conservatively based on the linear cell killing model. For the long lived ^{226}Ra and ^{228}Ra, our best estimate of attributable risk is 2.36 per 10^5 PY-μCi where PY are measured starting five years after exposure and μCi refer to systemic intake. For the short-lived ^{224}Ra, our estimate is 18 per 10^5 person-rad among juveniles and 10 per 10^5 person-rads among adults, where rads refer to average skeletal dose. Because the earlier paper (Sp70) indicated that effectiveness decreased with age within the juveniles, we have adopted the values 20 per 10^5 person-rad for ages 1-15 and 15 per 10^5 person-rad for ages 16-20. In view of the possibility of underascertainment, even these estimates assuming linearity are not necessarily conservative, but are the best available.

5.3 HEAD CARCINOMAS

Seventeen carcinomas of the mastoid air cells and paranasal sinuses ("head carcinomas") have been described (Ro78a) among the female radium dial painters. (Ten are mentioned in the MIT series and 26 in the CHR series, but the overlaps are not described). The data for the dial painters have been fitted to the same model as that used for the bone sarcoma cases, the only modifications being the assumption of a 10-year latent period in calculating person-years and the dosimetry described below (Figure 5.4). With the exponent c constrained to unity, the model gave an excellent fit with $\hat{b} = 1.98$ per 10^5 PY - μCi and $\hat{d} = 2334$ μCi ($\chi^2_3 = 2.73$, $P=.44$). No improvement in fit could be obtained by letting c run free.

It has been suggested that the primary mechanism for these carcinomas is the accumulation of the ^{222}Rn daughter of ^{226}Ra (Ev66). The measure of dose used for the dose-response fitting in this section is therefore based on the estimated systemic intake of ^{226}Ra only. This accumulation of ^{222}Rn would not occur for those exposed only to the isotopes ^{224}Ra or ^{228}Ra, possibly accounting for the absence of head carcinomas in the German injection series; on the other hand, the longer latent period of these cancers (19 to 52 years) suggests that insufficient time may have passed to observe this outcome in the German series.

5.4 OTHER EFFECTS

Only for lung, bone and head cancers are sufficient data available to characterize the shape of dose-response curves for alpha radiation. However several other somatic effects have been noted to occur with higher than expected frequency among exposed cohorts. For some of these effects an average exposure has been estimated, allowing an average risk index to be calculated, and for some a comparison between those with "higher" versus "lower" exposures gives greater credence to the association. These effects are summarized in Table 5.8 and described briefly below. Further details can be found in Appendix 1.

5.4.1 Cancers other than lung, bone or head

5.4.1.1 Gastrointestinal. Twenty-three cancers of the buccal cavity, pharynx, and gastrointestinal tract have been reported among the Newfoundland underground fluorspar miners (dV80) compared with 11.73 expected based on the surface workers, leading to an excess relative risk of 0.53 per 10^2 WLM. These data are consistent with a linear relation to exposure. None of the other studies of radiation-exposed mining populations report results for these diseases, so the finding has been neither confirmed nor refuted. One study of radium dial painters (Po78) found 10 cases of cancer of the large intestine compared with 4.96 expected but no dose relation amongst those whose exposures were measured.

5.4.1.2 Skin. Czechoslovakian uranium miners show 4.5-fold higher rates of skin cancer than the general population, increasing to eight-fold among those employed more than 10 years (Se78). While the estimated incidence of skin cancer in the general population must be considered with some skepticism, it is reassuring to note that a comparable group of other uranium workers not exposed to radon daughters showed a rate only 1.2 times higher than the general population (Se78). However, miners could show a duration-related excess because of exposures to agents other than radiation. Again these findings have been neither confirmed nor refuted in other studies of miners exposed to radon daughters. However, they are concordant with a recent revision of the estimate of epidermal thickness from 7 mg/cm^2 to 2-4 mg/cm^2 on certain parts of the body (Wh73), leading to the conclusion that alpha particles of energy 5.7 MeV or greater can result in irradiation of the basal layer (Ma74). For the long-service Czechoslovakian miners, an estimate of 1000-2000 rem to the basal layer produces a tentative excess relative risk of 0.47 per 10^2 rem or attributable risk of 0.76 per 10^6 PY-rem.

5.4.1.3 Female breast. Evidence from three studies of women exposed to radium is conflicting. Among those receiving injections of ^{224}Ra, five breast cancers have occurred compared to 1.21 expected, no breakdown by dose being provided (Sp78). Of the two systematic studies of radium dial painters, one found no excess of breast cancer (Po78) while the other found a relative risk of 1.51 for all women, rising to 5.71 among those measured with systemic intakes of >50 μCi (Ad80). The risk indices quoted in Table 5.8, based on small numbers, must therefore be considered to be highly tentative.

5.4.1.4 Liver. Both the German (vK78) and Portuguese (Ho74) thorotrast patients have suffered rates of liver cancer 20 to 38 times those in their respective control series. Although the amount injected is known, the dose to various tissues is more difficult to estimate, our best estimate for the liver being 500 rads (Appendix I). This leads to a tentative excess relative risk of 5 to 10 per 10^2 rads or an attributable risk of 135 to 216 per 10^6 person-rads.

5.4.1.5 Kidney. Three cases of kidney cancer have occurred among the radium injection patients compared with 0.6 to 1.1 expected (Sp78). No kidney cancers were found among the radium dial painters (Po78).

5.4.1.6 Leukemia. Both the radium injected patients and the dial painters show slightly more leukemia than expected, though even the combined excess is nonsignificant unless an additional three panmyelosis cases among the injection patients (who may have been misdiagnosed leukemia) are included. The thorotrast patients show substantial excesses of leukemia, though not as large as the excess of liver cancers. An estimate of dose to the bone marrow of 90 rads (Appendix I) leads to an excess relative risk of 7.7 per 10^2 rads (based on only two cases in the controls) or an attributable risk of 131 to 208 per 10^6 person-rads. For the atomic bomb survivors, BEIR80 has attempted to fit a linear-quadratic model for the gamma component and a linear model for the neutron component, thereby arriving at an estimate of 27.5 ± 7.5 cases per 10^6 PY-rads for the neutron effect (remarkably unaffected by how the gamma effect is modelled). These results are subject to the same reservations expressed in Section 5.1.1.6 and must be regarded as very doubtful because of uncertainty of the dosimetry.

5.4.1.7 Other cancers. No other sites have yet been reported to be associated with alpha radiation. However, to complete the picture, Table 5.9 summarizes the findings of the life span study of atomic bomb survivors for other sites (Be78a). For none of the remaining sites is the slope of the dose-response relation markedly larger at Hiroshima than at Nagasaki (though many of the tests for trend are more significant at Hiroshima because of the larger sample sizes). This suggests that any attempts to separate the gamma and neutron components are unlikely to be successful. Nevertheless, as most of the listed sites do show a relation to the T65 dose, these should all be considered potentially at risk from internal alpha emitters.

5.4.2 Other somatic Effects

5.4.2.1 Cirrhosis of the liver. Adult males injected with ^{224}Ra appear to show a dose-related excess of cirrhosis of the liver (Sp78). Though no external comparison is available, an internal comparison between those exposed above 14.3 μCi/kg (body weight) versus those below that figure leads to a relative risk index of

0.074 per 10^2 μCi. The thorotrast patients show substantially higher rates of cirrhosis but so do their controls. Based on the above estimate of 500 cumulative rads to the liver, we calculate an excess relative risk of 0.25 to 0.43 per 10^2 rads or an attributable risk of 21 to 63 per 10^6 person-rads.

5.4.2.2 Kidney Diseases. Adult males and females injected with ^{224}Ra show a small but dose-related excess of various kidney diseases (Sp78). Again only an internal comparison is possible, leading to an excess relative risk of 0.058 per 10^2 μCi or an attributable risk of 22.2 per 10^6 person-μCi.

5.4.2.3 Cataracts. Both adult male and juvenile radium injection patients show excesses of cataracts (Sp78). All 8 cataracts among juveniles are presumably radiation induced, leading to an attributable risk of 13.68 per 10^4 person μCi/kg. (Note that for juveniles, all indices are expressed in units of μci/kg whereas the adult indices are in units ofμCi.) For adult males, internal comparison leads to an excess relative risk of 0.28 per 10^2 μCi.

5.4.2.4 Growth retardation. Eighty-five of the 204 juvenile radium injection patients showed evidence of growth retardation, the fraction declining from 70% among those first injected between ages 1 and 5 to 12% among those first injected between 15 and 20 (Sp78). However, no internal or external comparisons are provided to allow calculation of risk indices. The point that the growth retardation, exostoses, or other endpoints may have been related to the underlying diseases (Section 5.2.2) merits reemphasis here (it will be recalled that the treatment was for, amonst other things, bone tuberculosis).

5.4.2.5 Benign exostoses. Thirty of the juvenile radium injection patients suffered exostoses (benign cartilagenous tumors of the bone), compared with about two expected (Sp78), leading to an excess relative risk of 1.27 per 10^2 rads or an attributable risk of 58 per 10^6 person-rads. These rates also declined with age, consistent with the decline in mean skeletal doses with age.

5.4.2.6 Cauda equina defects. Many fewer patients have been administered thorotrast for myelography, but in the only published series (McN68), 80% of those traced from hospital records were found to have progressive dysfunction or other serious deficits of the cauda equina, normally including paralysis of the lower limbs, as expected considering the massive doses (2 to 28 krad) to the lower end of the spinal canal from the thorotrast remaining even after attempts to remove it (Appendix I).

5.4.2.7 Chromosomal aberrations. The prevalence of complex chromosomal aberrations of somatic cells has been found to be significantly elevated among Colorado plateau uranium miners and plutonium workers of the Rocky Flats plant, and in both settings the aberration rate was found to be convexly related to exposure (Br78). Aberration rate indices of 4.00 per 10^6 cells-WLM and 2.26 per 10^4 cells-nCi Pu were estimated. The clinical importance of these changes is still unknown, but their assessment has been suggested as a biological marker for dose-response analysis and for comparison of the effects of different radionuclides. On the latter basis, the authors assert that the present standard for plutonium leads to a nine-fold higher aberration rate than the standard for radon daughters.

5.4.2.8 Premature aging. We have found no evidence of any dose-related nonspecific life shortening effect (i.e. not accountable by increases in mortality from specific causes). This question has been carefully examined both among the radium dial painters (St78) and the atomic bomb survivors (Be78b), for neither of whom were non-cancer deaths (or deaths other than bone or head tumors in the former) found to be in excess or to be dose-related.

5.4.3 Genetic effects

No human evidence seems to exist on any genetic effects of alpha radiation. Animal evidence is reviewed in Section 6.2.4.

TABLE 5.1

SUMMARY OF RISK ESTIMATES FOR LUNG CANCER UNDER LINEARITY

Setting	Reference	Mean WLM	PY at Excess Risk, or Number	Duration	Lung Cancer Deaths Observed	Expected	AR per 10^6PY-WLM (s.e.)	(RR-1) per 10^2WLM (s.e.)
Ertz mountain miners (19th century)	Ar67							
Joachimsthal		3840	NA		(9,500^1)	(9^1,^{2})	2.47	NE
Schneeberg		6480	NA		(18,000^1)	(9^1,^{2})	2.78	NE
Czechoslovakia uranium miners	Se76a	313	32,215^3		198^4	28.24^4	16.82 (1.40)	1.92^4 (0.16)
Colorado plateau uranium miners	Ar80	1180	32,196		159^4	25.24	3.52 (0.33)	0.45 (0.04)
Ontario uranium miners	He76	36	15,094	7^3	62^4	25.54^4	9.59 (2.07)	3.97^4 (0.86)
Newfoundland fluorspar miners	dV80	204^5 or 248^8	16,845^5		65	3.76^5 or 9.69^8	17.82 (2.35)	2.30^8 (0.34)
Swedish metal miners								
Kiruna, Fe	Jo73	110^5	1,900^5	15^5	13	4.47	2.72 (1.15)	1.74 (0.73)
Zinkgruven, Pb-Zn	Ax78	270^5	2,154^5		20	2.32^5	30.40 (7.69)	2.82 (0.71)
Malmberget, Fe	Re74	170^5	11,797		14	2.95^5	5.53 (0.63)	2.21 (0.75)
National Survey	Sn74	163	4,866	11	36	6.07	3.43 (0.69)	3.03 (0.61)
British iron miners	Bo70	260^5			36	20.58	N.E.	0.29 (0.11)
US metal miners	Wa63	620^5	25,033		47	16.1	1.99 (0.44)	0.31 (0.07)
Atomic bomb survivors	Be78a							
Hiroshima (1+rad)		38^6	644,600		152	109.5	1.74^6 (0.50)	1.02^6 (0.30)
Nagasaki (1+rad)		40^6	311,900		57	46.5	0.84^6 (0.61)	0.56^6 (0.41)

N.A. Not available.

N.E. Not estimable.

[1] Rate per 10^6 person-years

[2] Rate for British males 1900-1902, from Co79.

[3] Eliminating 10 years after first exposure.

[4] Based on a reduction of observed and expected deaths for latent period, see appendix.

[5] As quoted in BEIR80 and/or Ar78b but not reconciled with original source.

[6] Dose equivalent to the lungs, assuming Q=10 and organ dose estimates from Ke79, expressed in rems.

[7] Based on the 1-9 rad group as the standard and assuming that group was subjected to the mean excess relative risk per DE of the higher groups (see appendix).

[8] Based on internal rates scaled to the lowest exposure group (see Table K.4)

TABLE 5.2

VARIATION IN EXCESS RELATIVE RISK OF LUNG CANCER BY BROAD EXPOSURE CATEGORIES

Setting	Exposure (WLM)		Observed	Expected	(RR-1) per 10^2WLM (s.e.)
	Range	Mean			
Czechoslovakia	0 - 199	134	41	9.98	2.32 (0.48)
	200+	405	157	18.26	1.87 (0.17)
Colorado Plateau	0 - 599	243	38	11.77	0.92 (0.22)
	600+	2058	121	13.47	0.39 (0.04)
Ontario	0 - 59	19	35	21.48	3.31 (1.45)
	60+	125	27	4.06	4.52 (1.02)
Newfoundland	1-479	139	28	8.23	1.73 (0.46)
	480+	859	37	1.46	2.83 (0.49)
Sweden	2 - 112	36	9	3.56	4.24 (2.34)
	48+	343	27	2.51	2.84 (0.60)
Hiroshima	1 - 99[1]	16[1]	128	97.5	1.96 (0.73)[1]
	100+[1]	220[1]	24	12.0	0.45 (0.19)[1]
Nagasaki	1 - 99[1]	19[1]	41	37.6	0.48 (0.90)[1]
	100+[1]	127[1]	116	8.9	0.63 (0.95)[1]

[1] Dose equivalent to the lungs in rems, assuming Q=10 and organ dose estimates from Ke79.

TABLE 5.3

FITS OF LINEAR AND NONLINEAR MODELS FOR LUNG CANCER TO EACH STUDY SEPARATELY

General form: $RR = (a + bD^c)\ 0.5^{D/d_{\frac{1}{2}}}$

Data from tables A3.1 to A3.6

Studies	Estimate (s.e.) of parameters				Goodnes of fit		
	a	10^2b	c	$d_{\frac{1}{2}}$	chi square	df	P-value
Colorado plateau	1.00	0.43 (0.05)	1.00	∞	8.48	5	0.13
	1.00	3.07 (1.58)	0.74 (0.07)	∞	1.84	4	0.77
	1.00	0.55 (0.09)	1.00	11962 (6868)	4.52	4	0.34
	1.96	0.18 (0.04)	1.00	∞	3.71	4	0.45
Czechoslovakia	1.00	1.94 (0.15)	1.00	∞	2.49	3	0.48
	1.00	7.38 (3.24)	0.77 (0.07)	∞	0.45	2	0.80
	1.00	2.70 (0.16)	1.00	1351 (230)	0.14	2	0.93
	2.07	0.78 (0.19)	1.00	∞	0.99	2	0.61
Newfoundland	1.00	2.42 (0.41)	1.00	∞	10.40	7	0.17
	1.00	0.44 (0.55)	1.27 (0.19)	∞	7.47	6	0.28
Sweden	1.00	2.97 (0.31)	1.00	∞	0.84	3	0.84
	1.00	8.93 (1.56)	0.81 (0.03)	∞	0.04	2	0.98
	1.00	3.99 (0.24)	1.00	1484 (269)	0.05	2	0.97
	1.60	1.66 (0.35)	1.00	∞	0.37	2	0.83
Ontario	1.00	4.12 (0.52)	1.00	∞	1.29	3	0.73
	1.00	1.34 (0.84)	1.25 (0.13)	∞	0.46	2	0.79
	0.87	4.97 (1.49)	1.00	∞	1.12	2	0.57
Hiroshima[1]	1.00	0.61 (0.23)	1.00	∞	6.38	4	0.17
	1.00	1.16 (0.26)	0.41 (0.52	∞	0.25	3	0.97
	1.00	1.74 (0.66)	1.00	218 (66)	2.71	3	0.44
Nagasaki[1]	1.00	0.61 (0.05)	1.00	∞	0.02	1	0.89

[1] Dose equivalent in rems, assuming Q = 10 and organ dose estimates from Ke79

TABLE 5.4

FITS OF VARIOUS MODELS TO THE SIX STUDIES TOGETHER FOR LUNG CANCER

General form: $RR = (1 + b_1 D^c)\ 0.5^{-D/d_{\frac{1}{2}}}$

Data from Tables A3.1 to A3.6

Studies Included	Estimates (s.e.) of Parameters			Goodness of Fit		
	b^1	c	$d_{\frac{1}{2}}$	Chi square	d.f.	P-value
Five mining groups[2]	separate	1.01 (.14)	8454 (6288)	19.57	19	0.42
Five mining groups	separate	1.00	8774 (4776)	19.54	20	0.49
Five mining groups	separate	0.92 (.07)	∞	21.38	20	0.38
Five mining groups	separate	1.00	∞	23.46	21	0.32
Four showing sublinearity[3]	separate	0.79 (.07)	6189 (4310)	2.60	11	0.99
Four showing sublinearity	separate	1.00	2318 (496)	4.74	12	0.97
Four showing sublinearity	separate	0.72 (.04)	∞	3.06	12	0.99
Four showing sublinearity	separate	1.00	∞	13.16	13	0.44
Five mining groups[2]	common	0.60 (.24)	6665 (28,325)	128.40	23	0.0000001
All subgroups <300 WLM	common	1.00	∞	28.94	14	0.011
Four mining groups[4]	common	1.00	15,403 (8900)	30.03	18	0.04
Four mining groups	common	0.95 (.11)	∞	28.92	18	0.05
Four mining groups	common	0.00	∞	30.35	19	0.05

Notes

[1] Estimates of $10^2\hat{b}_1$ (separate) or $10^2 b$ (common) are given in Table 5.5.

[2] Colorado plateau, Czechoslovakia, Newfoundland, Ontario and Sweden.

[3] Colorado plateau (excluding 3720+ WLM Group), Czechoslovakia, Sweden and Hiroshima (assuming 1 WLM = 4 rem)

[4] Czecheslovakia, Newfoundland, Ontario and Sweden.

TABLE 5.5

RISK ESTIMATES FOR THE FIVE MINING POPULATIONS ASSUMING A COMMON EXPONENT OR CELL KILLING TERM

Setting	Mean exposure	Total number of excess deaths (number ≤ 300 WLM)	Estimate (s.e.) of $(RR-1)/10^2$WLM for models:		
			Linear	Nonlinear[1]	Cell killing[2]
Colorado plateau	1180	133.8 (10.6)	0.43 (0.04)	0.81 (0.45)	0.54 (0.08)
Czechoslovakia	313	169.6 (98.6)	1.94 (0.17)	3.17 (1.36)	2.01 (0.17)
Newfoundland	246	55.3 (9.4)	2.43 (0.36)	4.02 (1.85)	2.56 (0.36)
Sweden	163	29.9 (18.6)	2.91 (0.62)	4.78 (2.20)	3.05 (0.60)
Ontario	36	36.4 (36.4)	4.18 (0.85)	5.89 (2.19)	4.13 (0.80)
All subgroups ≤ 300 WLM	120	-- (173.6)	2.10 (0.25)	- -	- -
All except Colorado	250	291.2 --	2.21 (0.18)	3.06 (1.91)	2.28 (0.35)

[1] Model $RR = 1 + b_1 D^c$ where $\hat{c} = 0.916$ (0.952 for the common slope model).

[2] Model $RR = (1 + b_1 D)\, 0.5^{-D/d_{\frac{1}{2}}}$ where $\hat{d}_{\frac{1}{2}} = 8774$ (15,403 for the common slope model).

TABLE 5.6

RELATIVE RISKS PREDICTED BY THE THREE DOSE-RESPONSE MODELS

Basis of the fitted model	Cumulative exposure (WLM)	Predicted relative risk			Comparisons of (RR-1)s against linear model			
					Differences		Ratios	
		Linear	Nonlinear	Cell killing	Nonlinear	Cell killing	Nonlinear	Cell killing
Czechoslovakia study alone (Table 5.3)		$\underline{1+.0194D}$	$\underline{1+.0738D^{.770}}$	$\underline{(1+.0270D)(\frac{1}{2})^{D/1351}}$				
	10	1.194	1.435	1.264	+0.24	+0.07	2.24	1.36
	50	1.970	2.501	2.290	+0.53	+0.32	1.55	1.33
	200	4.880	5.364	5.776	+0.48	+0.90	1.12	1.23
	1000	20.400	16.068	16.762	-4.33	-3.64	0.78	0.81
Five mining groups with separate slopes:		$\underline{1+.0194D}$	$\underline{1+.0317D^{.916}}$	$\underline{(1+.0201)(\frac{1}{2})^{D/8774}}$				
Czechoslovakia estimate (Table 5.5-top)	10	1.194	1.261	1.200	+0.07	+0.01	1.35	1.01
	50	1.970	2.141	1.997	+0.17	+0.03	1.18	1.03
	200	4.880	5.063	4.941	+0.18	+0.66	1.05	1.02
	1000	20.400	18.744	19.497	-1.66	-0.90	0.91	0.95
Four mining groups with common slope (Table 5.5-bottom)		$\underline{1+.0221D}$	$\underline{1+.0306D^{.952}}$	$\underline{(1+.0228D)(\frac{1}{2})^{D/15403}}$				
	10	1.221	1.274	1.227	+0.05	+0.01	1.24	1.03
	50	2.105	2.268	2.135	+0.16	+0.03	1.15	1.03
	200	5.420	5.746	5.510	+0.33	+0.09	1.07	1.02
	1000	23.100	22.965	22.753	-0.14	-0.35	0.99	0.98

TABLE 5.7

FITS OF LINEAR AND NONLINEAR CELL KILLING MODELS TO THE BONE SARCOMA DATA

general form: $R = bD^{c}0.5^{D/d_{\frac{1}{2}}}$

Study	Estimated Coefficients			Goodness of Fit		
	10^5b	c	$d_{\frac{1}{2}}$	Chi square	d.f.	P-value
Female Dial Painters	2.36	1	2,068	9.43	5	.09
(Ro78a)	0.020	2.21	578	0.82	4	.94
German patients (Sp78,Ma78)						
Juveniles	18.13	1	38,085	3.08	3	.38
	0.0072	2.25	909	1.49	2	.47
Adults	10.03	1	∞	1.19	3	.76
	2.44	1.25	∞	0.84	2	.66
Combined	17.9/10.1	1	42,787	4.29	6	.64
(Juvenile/adult)	.60/.50	1.55	1,909	2.81	5	.73
M.I.T. Series (Ev74)						
All subjects	10.68	1	9,342	7.17	5	.21
	0.20	1.53	5,131	3.51	4	.48
"Suitable" only	7.78	1	5,037	6.11	5	.30
	0.016	1.90	1,978	2.48	4	.65
C.H.R. Series (Ro78b)						
All subjects	8.60	1	10,615	6.82	4	.15
	0.74	1.34	6,139	4.87	3	.18
Listed painters only	6.68	1	29,749	2.42	4	.66
	0.017	1.79	5,854	1.11	3	.77

TABLE 5.8

SUMMARY OF EPIDEMIOLOGIC EVIDENCE ON OTHER POTENTIAL SOMATIC EFFECTS OF ALPHA RADIATION

Effect	Population	Reference	Number of cases Observed	Number of cases Expected	Relative Risk	Risk Index	Evidence of Dose-Relation
Neoplasms other than lung, bone or head							
Gastrointestinal	fluourspar miners	dV80	23	11.73	1.96	0.53[1]	yes
large intestine	dial painters	Po78	10	4.96	2.02	—	no
skin	Czech uranium miners	Se78	(103.8)[2]	(13.0)[2]	7.98	0.47[15]	duration only
breast	radium injections	Sp78	5	1.21	4.13	0.28[4]	n.r.
	dial painters - all	Ad80	36	23.77	1.51	—	—
	- measured		6	1.04	5.75	0.77[4]	yes
	dial painters - all	Po78	9	9.45	(0.95)[5]	—	no
liver	thorotrast patients	vK78	107	5.38	19.88	3.78[3]	n.r.
	thorotrast patients	Ho74	64	1.69	37.78	7.36[3]	n.r.
kidney	radium injections	Sp78	3	0.60	(5.00)[5]	—	n.r.
leukemia	radium injections	Sp78	5[6]	0.84	5.95	0.46[4]	n.r.
	dial painters	Po78	3	1.41	(2.13)[5]	—	insufficie data
	thorotrast patients	vK78	17	2.15	7.91	7.67[3]	n.r.
	thorotrast patients	Ho74	23[7]	(1230)[8]	(18.70)[8]	208[11]	n.r.
	Hiroshima survivors	BEIR80	68	16.06	4.23	27.5[9]	yes
Other somatic effects							
liver cirrhosis	radium injections	Sp78	9[10]	4.65[10]	1.94	0.074[4]	yes
	thorotrast patients	vK78	126	39.82	3.16	0.43[3]	n.r.
	thorotrast patients	Ho74	23	10.17	2.26	0.25[3]	n.r.
kidney diseases	radium injections	Sp78	16[10]	9.14[10]	1.75	0.058[4]	yes
cataracts	radium injections - juveniles	Sp78	8	(204)[8]	(39.22)[8]	13.68[16]	n.r.
	- adult males		7[10]	1.55[10]	4.52	0.28[4]	yes
tooth breakage	radium injections - juveniles	Sp78	23	(204)[8]	(112.7)[8]	39.33[16]	n.r.
growth retardation	radium injections - juveniles	Sp78	85	?	—	—	n.r.
benign exostoses	radium injections - juveniles	Sp78	30	2.00	15.00	1.27[3]	n.r.
cauda equina defecit	thorotrast myelography	McN68	12	(15)[8]	(800)[8]	—	n.r.
complex chromosomal aberrations	US uranium miners	Br78	(92)[12]	(16)[12]	5.75	4.00[13]	yes
	US plutonium workers		n.r.	n.r.	—	2.26[14]	yes

Footnotes - see next page.

Notes to Table 5.8

n.r. - not reported.

1. $(RR-1)/10^2$WLM.
2. Rates per 10^4 miners among those working more than ten years (8 year period at risk)
3. $(RR-1)/10^2$rad.
4. $(RR-1)/10^2$ μCi.
5. RR not significantly different from unity.
6. Includes 3 cases of panmyelosis.
7. Includes 8 cases of aplastic anemia and 3 of other blood dyscresias.
8. Expected cases near zero: numbers in parenthesis are the number at risk and AR per 10^3 persons.
9. AR/10^6 PY-rad kerma (neutrons) estimated by weighted least squares fitting of the "LQ-L" model to the Hiroshima and Nagasaki data.
10. Observed cases among those with >14.3 μCi/kg ^{224}Ra; expected cases based on the observed cases <14.3 μCi/kg.
11. AR/10^6 person-rads.
12. Numbers of complex aberrations observed in 7926 cells examined (not number of affected workers).
13. Aberrations/10^6 cells - WLM.
14. Aberations/10^4 cells - nCi Pu.
15. $(RR-1)/10^2$ rem to the basal cell layer.
16. AR/10^4 μCi/kg

TABLE 5.9

RELATIVE RISKS OF CANCER AMONG ATOMIC BOMB SURVIVORS

(Life Span Study Results to 1974, adapted from Be78a)

Site of Cancer (ICD codes)	City	Number of cases	Risk Relative to 0-rad*group		P-value for linear trend
			1-99 rad	100+ rads	
Leukemia (204-207)	Hiroshima Nagasaki	110 34	1.51 1.54	13.82 11.70	.000 .000
Digestive (150-159,197)	Hiroshima Nagasaki	1971 455	0.94 1.19	1.22 1.16	.002 .157
Lung (162)	Hiroshima Nagasaki	257 73	1.31 1.09	2.00 1.80	.002 .286
Breast (174)	Hiroshima Nagasaki	78 24	1.01 1.28	2.37 2.07	.017 .156
Cervix & Uterus (180-182)	Hiroshima Nagasaki	227 55	1.34 1.76	1.27 1.10	.103 .824
Urinary (188-189)	Hiroshima Nagasaki	73 12	0.95 3.82	2.37 3.65	.058 .141
Lymphatic (200-203,208,209)	Hiroshima Nagasaki	53 22	0.79 0.82	1.92 1.15	.018 .048
All Others (140-149,170-173, 183-187,190-196, 197-199)	Hiroshima Nagasaki	250 56	0.93 0.97	1.44 1.42	.044 .405

* Kerma doses in air

TABLE 5.10

SUMMARY OF THE MAJOR EPIDEMIOLOGICAL FINDINGS

Study	Strengths	Limitations	Conclusion on Shape of Dose-Response Relation
Lung cancer			
Czechoslovakian uranium miners (Sv76,Ku78a,Ku79)	Dosimetry Large sample size at moderate doses Relatively long follow-up	Inappropriate statistical analysis	Approximately linear
Colorado plateau uranium miners (Ar76,Ar78,Ar80)	Large sample size - Good follow-up Well analyzed Smoking and other modifiers available	Poor dosimetry Very high doses	Strongly convex Smaller slopes than other studies
Ontario uranium miners (Ha76,He76)	Large sample size Very low doses	Short follow-up Probable underascertainment Poor dosimetry	Approximately linear
Newfoundland fluorspar miners (dV80)	Moderate doses Long follow-up	Very poor dosimetry No suitable external reference Latency ignored	Slightly concave
Swedish metal miners (Sn73)	Very long follow-up	Small sample size Heterogeneous exposure groups No description of methods	Convex
Atomic bomb survivors (Pe78a,b)	Very large sample size Moderate doses Good follow-up	Gamma effects Differential "survival of fittest"? Diagnostic unreliability Relevance of acute-neutron to chronic-alpha inferences	Very strongly convex
Bone sarcoma and head carcinoma			
Radium dial painters (Ro78a)	Very long follow-up	Incomplete tracing Dosimetry	Bone: concave Head: linear
Radium-injected patients (Sp70,Sp78,Ma78)	Good dosimetry Good tracing Follow-up long relative to latency Dose fractionation and age effects	Possible effects of original diseases or their treatment	Linear
Liver tumors, cirrhosis and leukemia			
Thorotrast patients	Moderately long follow-up Hospital comparison groups	No comparison of doses Incomplete tracing Possible effects of original diseases	Excess risks, but shapes not described

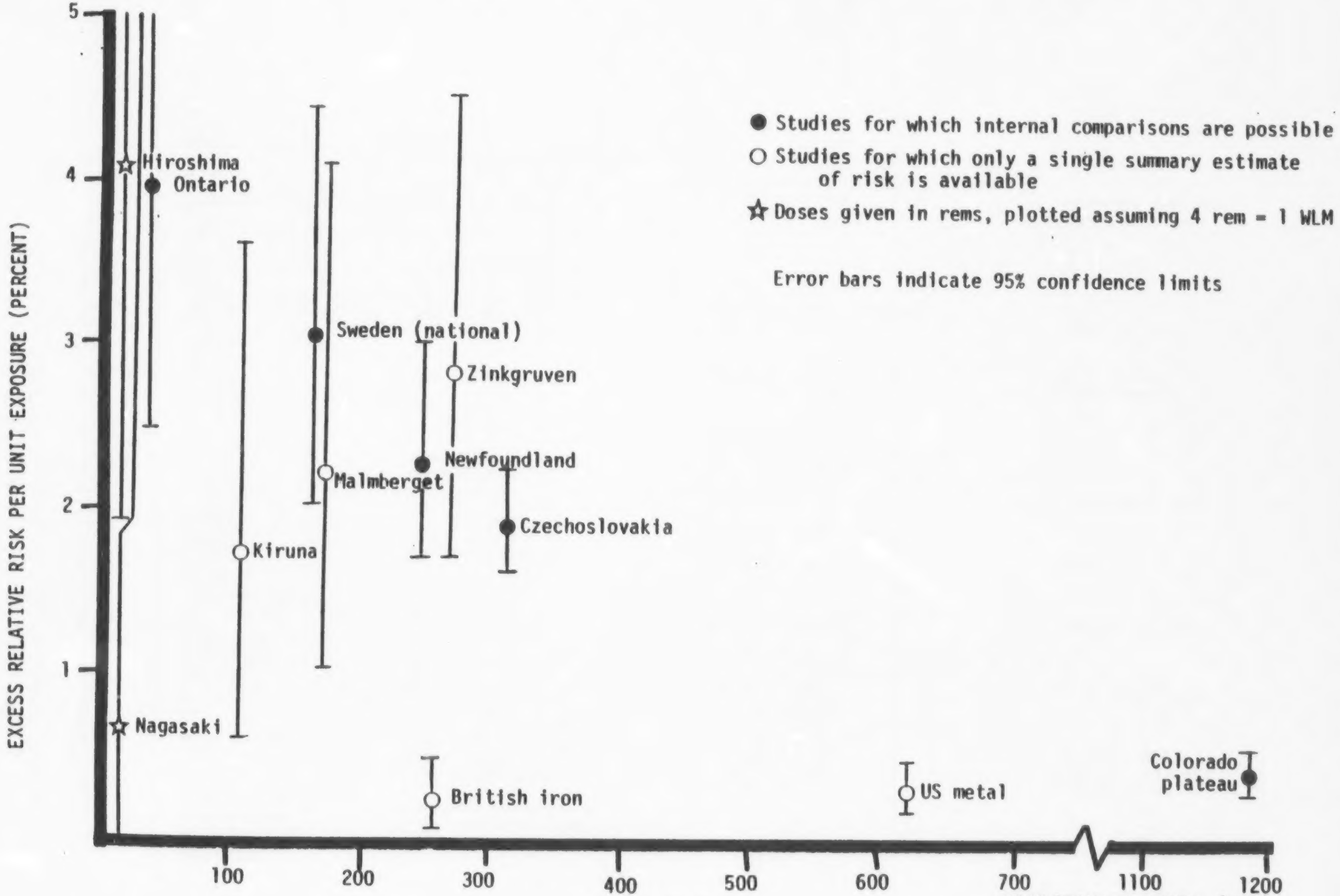


FIGURE 5.1

COMPARISON OF AVERAGE RISK ESTIMATES BETWEEN STUDIES

FIGURE 5.2
RISKS OF LUNG CANCER WITHIN EACH OF SIX POPULATIONS

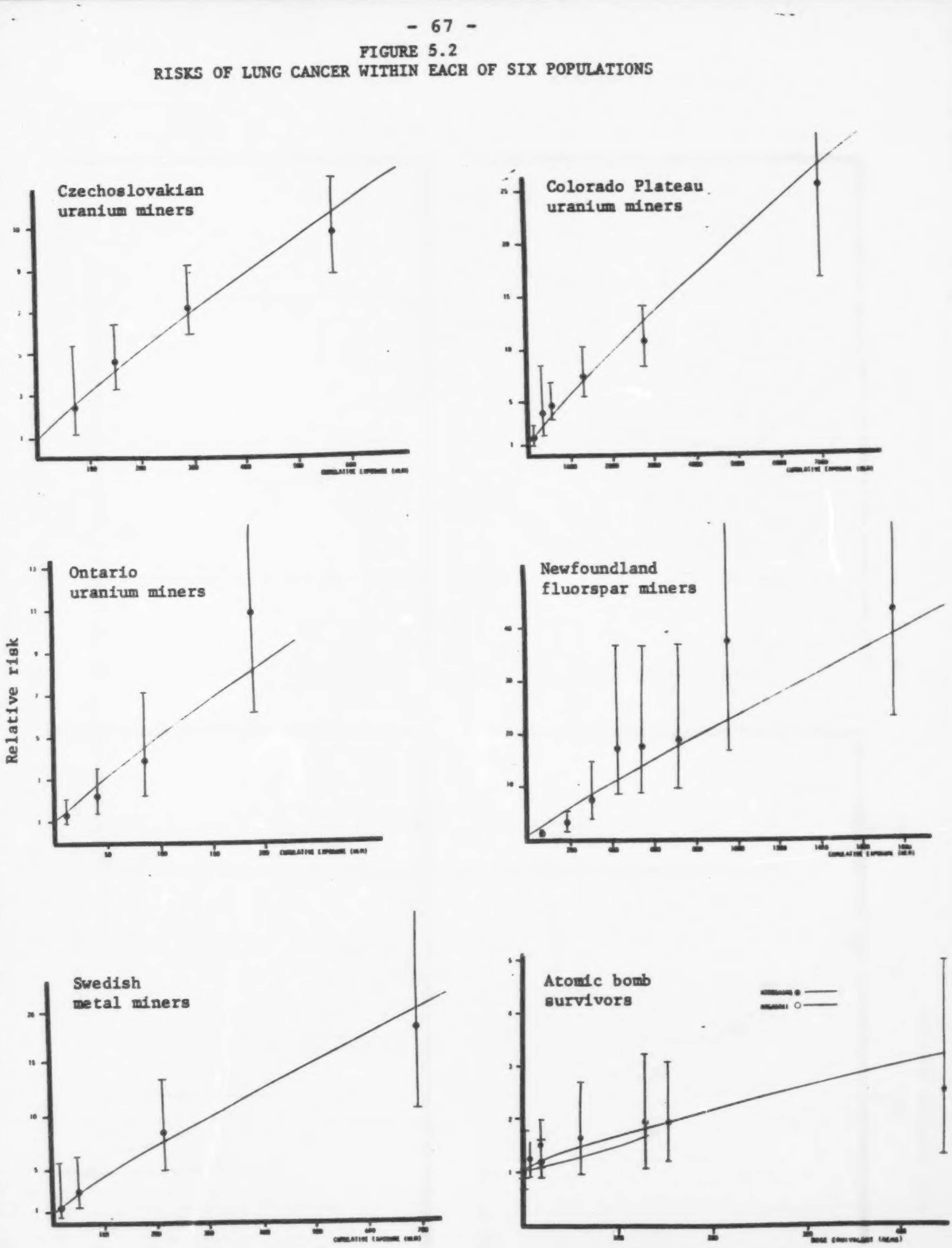


FIGURE 5.3
BONE SARCOMAS AMONG RADIUM-EXPOSED PERSONS

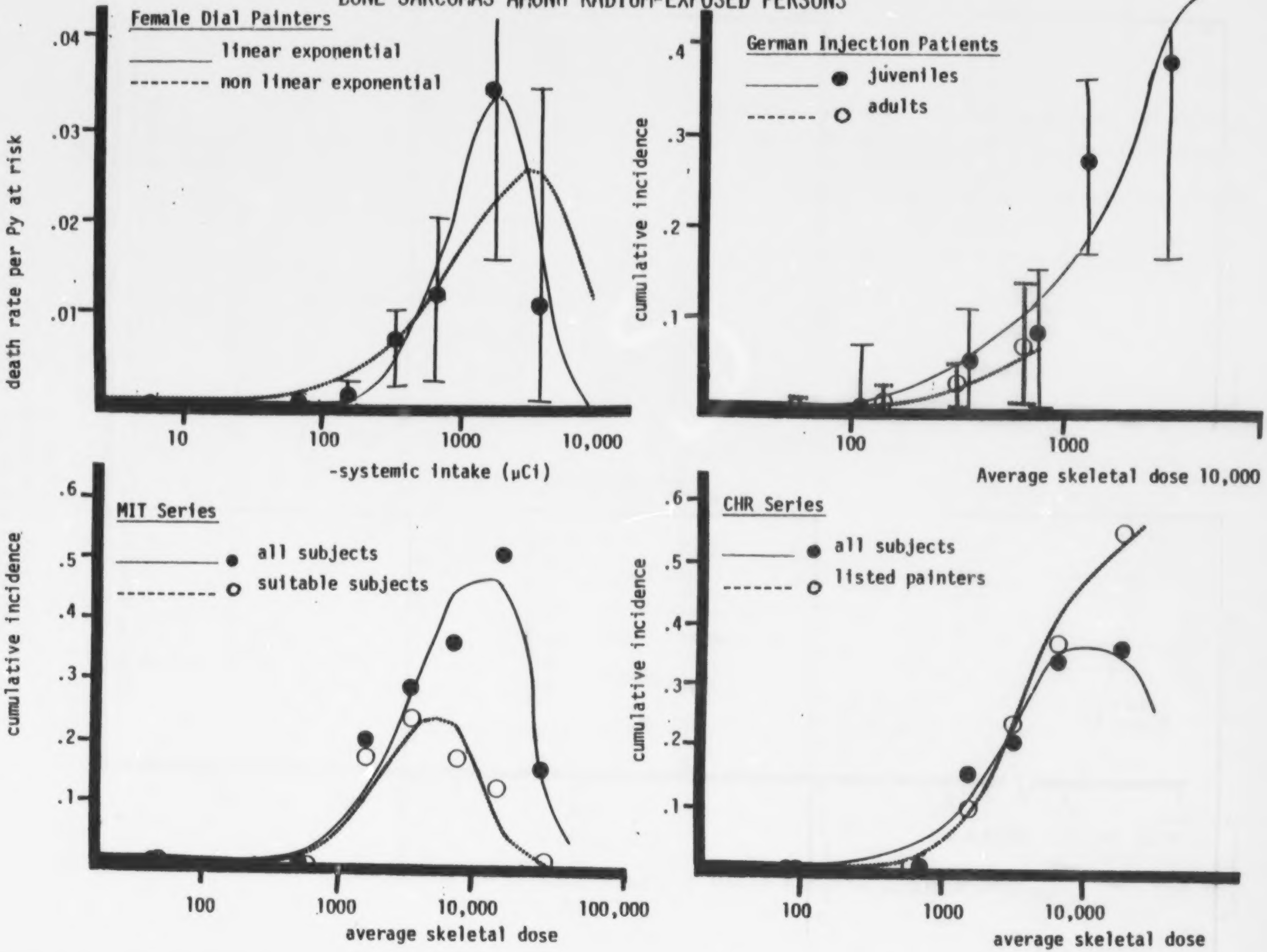
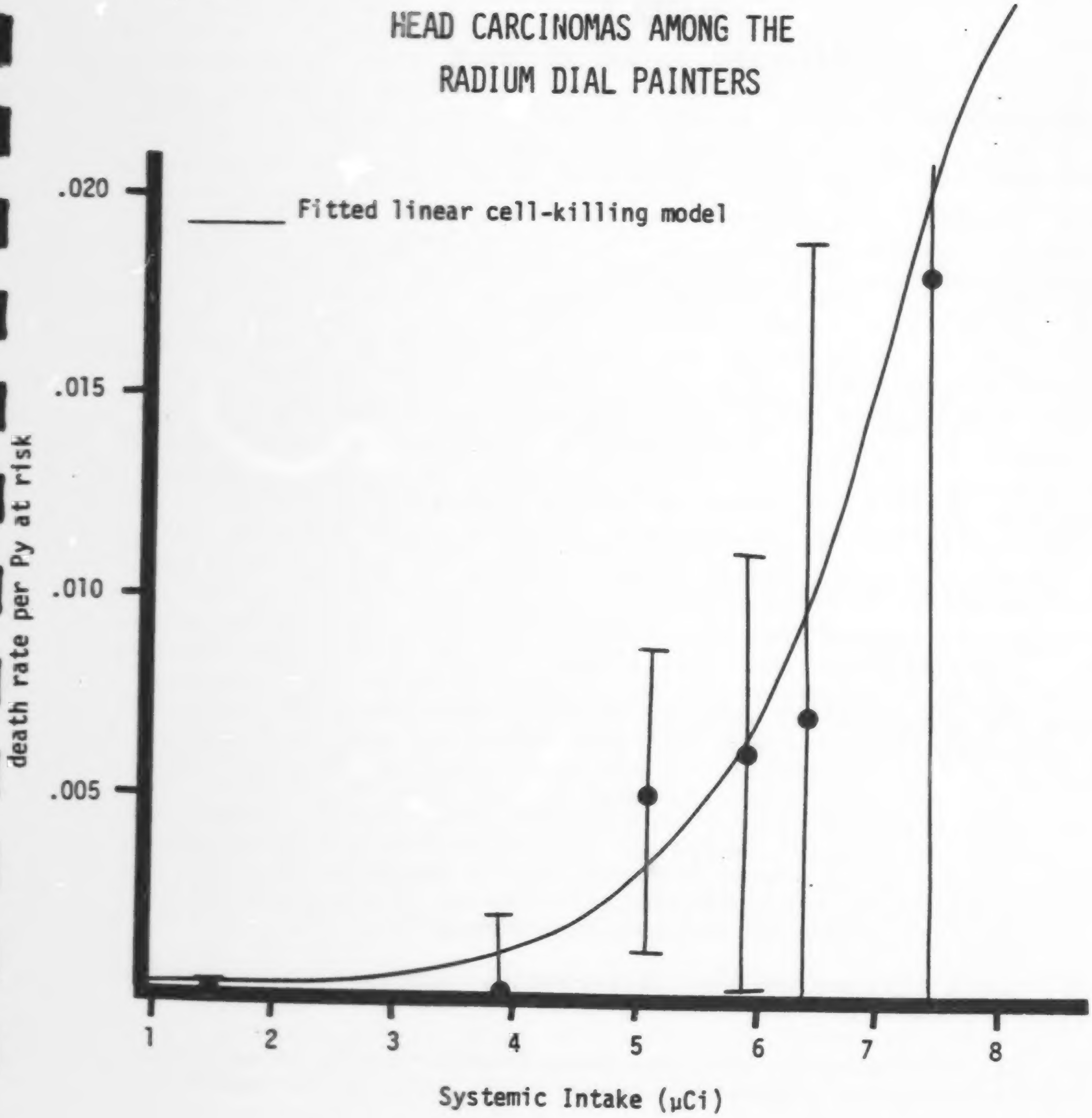


FIGURE 5.4
HEAD CARCINOMAS AMONG THE
RADIUM DIAL PAINTERS



CHAPTER 6

EXPERIMENTAL ANIMAL EVIDENCE

6.1 INTRODUCTION

6.1.1 Scope

In this chapter, we attempt to summarize the literature on experimental induction of cancer in animals by high-LET radiation. Studies which deal only with low-LET radiation are not included, but both internal alpha emitters and external neutron irradiation have been reviewed (the latter only qualitatively). We have not attempted to search systematically for references but have taken the excellent review in Annex I of UN77 as our starting point, together with a few other review articles. Furthermore, we have limited our investigation to those papers in scientific journals or readily available books and conference proceedings. Thus we make no claim to having completed an exhaustive review of this literature, though we feel it probably includes all of the most commonly cited studies.

6.1.2 Objectives of Animal Studies

It is generally agreed that the problems of extrapolation between species preclude any use of animal studies for providing quantitative risk estimates in man except perhaps for comparing the relative potencies of various carcinogens (Cr81). While some experimental work is aimed at understanding the fundamental mechanisms of carcinogenesis, we are not concerned here with this application. Instead, the relevance of experimental studies to setting standards in man is through quantifying forms of relationships and their modifying factors in order to suggest appropriate statistical models for analysis or qualification of epidemiological data. In particular, some of the factors which have received the attention of investigators are:

1. The overall shape of the dose-response curve, particularly at low doses;
2. The role of temporal factors: dose fractionation, dose rate, duration, age at exposure, age at risk, time since exposure;
3. Latent periods: their distribution and dependence on dose or dose rate;
4. The relative biological effectiveness (RBE) of neutrons or alpha particles and its dependence on dose;
5. The relative sensitivity of different organs to different types of radiation and modes of application; and

6. The interaction (synergy) of radiation effects with other carcinogens.

In this chapter we deal only with objective (1), whereas objectives (2), (3) and (6) are discussed in combination with the human evidence in the following chapter. Inasmuch as high and low-LET radiation have different slopes of dose-response curves, the RBE will of course vary with dose (objective 4), but we feel an adequate description of this phenomenon would have required us to characterize the low-LET curve and this was beyond the scope of our report. We have chosen to organize our findings on a site-by-site basis, but have not attempted to compare explicitly the relative sensitivities of the different organs (objective 5). Also under objective 5, several studies have compared various modes of application (e.g. intravenous vs. intratracheal injections of different suspension media) but we feel these issues are largely irrelevant to humans; for these studies, we have concentrated on the dose-response data within each mode of application, pooling where appropriate.

6.1.3 Limitations of Animal Studies

As noted above, animal studies are useless for providing risk estimates for man. However, some scientists (e.g. Ra80) feel that we should also be cautious about applying to humans animal evidence on the factors described above. Some of their considerations are the following:

1. There are qualitative differences between cancers at the same site in different animals, suggesting different mechanisms;
2. Animal strains used are generally highly inbred, whereas the greater heterogeneity in susceptibility among humans might tend to increase their response rates at low doses thereby changing the slope of the dose response curve (cf. Sections 2.4.2 and 7.7, Appendix F, and Ba73);
3. Animal life spans are short and latent periods a much larger fraction of their life, possibly reducing response rates to a greater extent than in humans; if latent periods are dose related, this reduction would be more marked at low doses, thereby altering the slope of the dose-response curve more in animals than in humans;
4. Experimental conditions protect animals from the many cancer initiating and promoting agents to which humans are presumably exposed; this also is likely to produce concave relationships as the experimental carcinogen would have to provide both initiating and promoting factors.

These considerations lead Radford to suggest that experimental dose-response curves are likely to be more concave (or less convex) than for humans. (The reverse position might also be argued, though we have not seen it done.) With these arguments in mind and on grounds of conservatism, we have looked particularly for studies which suggest relationships contrary to those predicted by Radford's argument, especially studies showing convex relationships at low doses.

6.1.4 Methodological Considerations

We have not attempted to evaluate critically the methodology of each of the studies examined. We briefly enumerate here some of the criteria which need to be considered; a thorough discussion of these considerations is contained in Section 1, Annex I of UN77.

1. Radiation quality: neutron or alpha particles;
2. For alpha particles, the particular radionuclide, its chemical form and suspension medium; for neutrons, their energy.
3. Mode of application (injection, ingestion, inhalation or external);
4. Range of doses studied;
5. Exposure pattern: dose rate, fractionation and duration;
6. Experimental animals used;
7. Target sites most heavily affect. (We are not particularly interested in compiling an exhaustive list of effects as these would probably vary between species, but merely with finding experimental models which might be relevant to man);
8. Response parameters investigated: cumulative incidence, mean tumors per animal, nonspecific lifespan shortening, latent period, RBE, interactions with other carcinogens or modifying factors (age, fractionation, etc.);
9. The period of observation, in relation to the latent period, the lifespan of the animals, and survival from the acute effects of the radiation;
10. Methods of analysis: as in the epidemiologic literature, the statistical methods used have been quite variable. In an attempt to bring some order to this, we have standardized our methods of reporting by reanalyzing the data as described in the next section.

6.1.5 Methods of Analysis

Our methods of data presentation have had to be adapted to suit the extent and comparability of the data available to us from the various studies. For lung cancer, none of the studies provide enough data points to allow fitting so we have treated these data descriptively. On the other hand, for bone sarcomas and skin cancers in relation to alpha emitters, there are numerous studies providing sufficient data for model fitting. We have presented all of these in the form of a fit of the entire data set to a linear model with linear and quadratic cell killing terms, followed by a comparison of observed sarcomas at "low doses" with those predicted by the model, where we have chosen two arbitrary cutoffs for each study to define "low". The fitting procedure is essentially the same as used for the epidemiologic data (Section 4.2.1.3 and Appendix J) with the modification described below. For completeness, we include a qualitative description of the main conclusions of the studies of neutron irradiation, but have not attempted any model fitting or quantitative description as that would have been beyond the scope of this report; indeed, the diversity of ways these data have been described effectively precludes any systematic quantitative description or analysis.

Experimental data differ from the epidemiological data in one important sense affecting analysis. Rather than presenting observed cases in relation to subject-time at risk which can be used to estimate rates (R, Section 4.1.1), either cumulative incidence (CI) at the time of death or some earlier predetermined time of sacrifice, T, or average numbers of tumors per animal (AT) at T are provided. These are related to the instantaneous incidence rate, R(t), as follows (Sh74):

$$AT(T) = \int_0^T R(t)dt = \overline{R}T \text{ where } \overline{R} \text{ is the average rate} \quad [6.1]$$

$$CI(T) = 1 - \exp[-AT(T)] \quad [6.2]$$

or equivalently

$$\overline{R} = AT(T)/T \quad [6.3a]$$

$$= -\ln\,[1-CI(T)]/T \quad [6.3b]$$

The studies of lung and bone cancer have all provided data on cumulative incidence. Had we attempted to model CI as a function of dose, we would have encountered the problem that CI is bounded by unity and to avoid this constraint, our model might have underestimated risks at lower doses. Instead we have used the empirical complementary log transformation [6.3b] for describing average incidence rates $\overline{R}$ in relation to dose, or have used equation [6.2] directly for fitting a model expressed in terms of $\overline{R}$ to the cumulative incidences. (Note that the latter can be done even when CI = 1 in some groups, whereas [6.3b] would produce an infinite estimate of $\overline{R}$ in these groups.) The general model we have used for fitting is essentially the same as was used for the epidemiologic data, with the addition of a quadratic cell killing term because of the larger number of data points in the dose range where it might be relevant: thus

$$\overline{R}T = (a + bD^c)e^{-fD-gD^2} \quad [6.4]$$

The parameter a was constrained to the rate in the unexposed group and this group was not included in the fitting. Preliminary analyses indicated that c could not be estimated with any precision, so in the tables which follow we have constrained c to unity and instead tested departures from model [6.4] by comparing the observed (O) with predicted (P) cases out of all cases (N) at "low" doses, using a continuity-corrected chi square test:

$$\chi^2 = \frac{(|O-P|-1/2)^2 N}{P(N-P)} \qquad [6.5]$$

In all these analyses, we have ignored the probable variation in T between exposure groups because the necessary data were rarely provided. Obviously as doses become larger, the lifespan of the animals becomes shorter due to mortality from other radiation-related competing risks. Failure to take account of this may have caused $\bar{R}$ to be underestimated at higher doses, particularly if R(t) is a strongly increasing function of time (as with most tumors), and may thus have introduced a spurious convex tendency into our findings. Only two of the studies we have seen (Sh74, on neutron irradiation and Bu68 on alpha radiation and skin tumors) have taken adequate account of the structure of incidence data as expressed in equations [6.1] and [6.2]. Both authors have recognized that cumulative incidence at a single fixed point in time is relatively insensitive (because it ignores the times at which the events occurred) and possibly biased (because of the variation in times at risk). To obtain maximum precision and eliminate that bias, both authors have estimated AT(T) using equation [6.1] where R(t) was calculated taking into account the actual numbers of animals still at risk at each point in time.

On the other hand, a common fallacy in many of these studies, particularly those of bone tumors, consists of relating risk to cumulative dose at death, which obviously increases with lifespan. This procedure will tend to shift the curve at high doses to the left thereby introducing concavity. To avoid this bias, we have used the applied dose or the cumulative dose evaluated at some fixed interval after exposure for all analyses.

6.2 FINDINGS FOR ALPHA EMITTERS

6.2.1 Lung Cancer

Table 6.1 summarizes data from six studies of lung cancer in relation to a variety of alpha emitters administered in a variety of ways. All show a decreasing effectiveness with increasing dose, some markedly so. However, a number of qualifications need to be made before concluding that these data imply convexity at low doses. (1) Unlike certain other tumors considered below, lung cancer is not uncommon in these species, but only three of the six studies include a control group which could be used to established the intercept. Where such an estimate is available (Li75, Le72, Yu67), we have subtracted this from the transformed incidence rate in the other groups of these animals but otherwise have assumed the natural incidence was zero. The effect of underestimating the natural incidence would be to exaggerate the convexity (Section 4.2.1, Figure 4.2). (2) In most studies, the numbers of cancers at low doses is small, leading to large variability. (3) With so few data points, it is virtually impossible to determine whether the convexity is due to cell killing or to low-dose nonlinearity. It is certainly plausible that the dose at which cell-killing begins to become important would vary between radionuclides, modes of application, and species of animal. (5) Each study uses a different index of cumulative exposure, and some may be less appropriate measures of "effective dose". Obviously accumulation of exposure to death suffers both from the problem of "wasted doses" (Section 4.2.1) and the bias that longer survival implies higher doses if the exposure were chronic (Section 5.1.1.1 and 6.1.5). (6) In some cases, there is little variation in response rates (e.g. Ch76 group "C" and Le72 "nitrate") so obviously response per unit dose will be inversely related to dose.

In summary, lung cancer incidence depends convexly on alpha radiation, but there is as yet insufficient reliable data at low doses to determine whether this convexity is merely a cell-killing effect becoming apparent at several hundred rads (several thousand rems).

6.2.2 Bone sarcoma

Seven papers have described the cumulative incidence of bone sarcomas in relation to internal alpha emitters in sufficient detail to allow model fitting (Table 6.2 and Figure 6.1). Five of these have been summarized in a review by Mays and Lloyd (Ma72) and these data were used as quoted there. Table 6.2 is adapted from the summary table in that review with two important modifications.

First, whereas Mays and Lloyd arbitrarily selected a subset of the data in which the response appeared to be approximately linear and estimated the slope as the average excess (beyond control) risk in that subset divided by the mean dose, we have used weighted least squares to fit the cell killing model (equations [6.2] and [6.4]) to the entire dose range. We have chosen this approach to avoid arbitrariness in selecting the linear range and to improve the precision of the estimated low-dose slope by basing it on more data. In testing the fit at "low doses", arbitrariness is again involved in selecting the cutoff point. To describe more fully the deviation from linearity, we have chosen the two cutpoints for each study which in our judgement best characterize any deviations that are apparent.

Second, as noted earlier (Section 6.1.5), Mays and Lloyd use cumulative dose one year before death (among the sarcoma cases) as the exposure variable. As the ratio of cumulative to early radiation dose decreases strongly with increasing initial dose of radioactivity (due at least in part to shortening of life span), this produces a spurious convexity in all their findings. When injected dose of radioactivity (in μCi/kg) instead of cumulative dose is used as D in model [6.4], the fit is in every case improved, often substantially.

Of the 13 studies described, six showed at least suggestive ($p>0.10$) departures from the cell killing model, either by the overall test of fit or in one or more of the low dose ranges. Two of these (Mu78a and Bu70) showed lack of fit by the overall test but not at low doses (due to excessive variability in response at higher doses) whereas two (Le72 and Fi62) showed significant nonlinearity (at one of the low dose cutoffs) which was diluted in the overall test. For the two remaining studies (Go71a and Mu78c), the two criteria were concordant. Of the 13 studies, three showed excellent fits to the cell killing model, four showed consistent concavity (though only one (Fi62) was significant, and that only at one cutpoint), and six showed some degree of convexity (two [Go71a and Mu78c] at both cutpoints, several showing variable patterns including some lack of fit at higher doses). We were unable to discern any consistent pattern to these departures in terms of radionuclide, animal, dose range or any other feature.

However, two of the studies for which the two tests were discordant merit particular comment. In both of these, several experimental conditions were manipulated, with only a few dose categories within each choice of conditions, thereby precluding a separate fitting within each subgroup and requiring a pooled analysis.

In the study of ^{237}Np (Le72), a factorial array of two modes of application (intravenous and intratracheal), two chemical forms (nitrate and oxylate), two sexes and four dose groups was used. A preliminary multi-way contingency table analysis using log linear models (Bi75) suggested that these four factors affected risk multiplicatively with no three- or higher-way interaction. Therefore, model [6.4] could be fitted to all the data by merely multiplying the slope parameter b by $e^{m_i+c_j+s_k}$ where m_i, c_j and s_k were additional parameters for the effects of method, chemical and sex. In the lowest two dose categories, the predicted events were so small (<1) that some further pooling of the data was needed. Combining all eight groups at the lowest dose level and all four groups for each method at the next dose level led to significantly more events observed than predicted in the lowest group but otherwise an excellent fit to the data. However the possibility that this model was inadequate should be kept in mind.

In a study of ^{239}Pu (Bu70) a variety of modes of application and chemical forms was also used, but not arranged in such an elegant experimental design. Only five of these subgroups allowed any internal comparisons of different doses and in two of these only one sarcoma was observed. However all doses were low (maximum 76 rads) so a linear slope could easily be estimated within each of the three subgroups having sufficient cases, without requiring least squares fitting. This was then used to obtain the expected numbers in the lower categories of each subgroup and the observed and predicted numbers were then pooled over the five subgroups. The overall test showed suggestive lack of fit because of a highly variable pattern of excesses and shortfalls, no single choice of cutpoint showing significant departure from linearity.

In summary, we must conclude that though there is evidence in support of both convexity and concavity, no clear patterns emerge and in general linearity is unlikely to be far from the truth.

Issues of shapes of relations aside, there are interesting differences in slopes between the different nuclides. Taking ^{226}Ra as the standard, the relative biological effect of ^{228}Th was much greater (10 times) per rad than was ^{226}Ra, ^{239}Pu was next most effective and then ^{228}Ra (2 to 3 times). In contrast the beta rays from ^{90}Sr were less effective, rad for rad, than the alpha rays from ^{226}Ra. These relative effects are explained by the facts that whereas Th and Pu are deposited on the surface of bone, and thus able to irradiate the actively growing cells, Ra (and Sr) are deposited throughout the volume of the bone, and most of their alpha (or beta) energy is "wasted" on bone mineral. The difference between the relative effects of Th and Pu may be due to a number of features - different energy of alphas, different dose rates for the same rad dose (due to greatly different half-lives) or to effects secondary to a radiation nephritis induced by the Th, which is picked up by the kidney more than is the Pu.

6.2.3 Skin tumors

Only one study of skin tumors in relation to alpha radiation (Bu68) was found. This showed a very poor fit to the cell killing model (Figure 6.2), summarized by a chi square of 39.08 on 7 degrees of freedom ($p<0.001$). The three lowest categories showed fewer than predicted tumors suggesting low-dose concavity, but the major contributions to lack of fit came from the great variability in response at high doses. The addition of the exponent c in model [6.4], while producing an estimate of $\hat{c} = 1.3$ (with a standard error of 15.9), did not improve the fit. Thus no single model is likely to fit these data and we are unable to interpret the findings.

6.2.4 Genetic effects

Genetic damage may be to either one of the paired chromosomes; the twinning properties of the double helix of DNA makes it more likely that with high LET radiation the radiation effect will be linear with dose, in contrast to the situation with low LET radiation, where a quadratic effect is more probable on theoretical grounds (see Chapter 3, section 3.2). For alpha emitters, irradiation of the gonads will primarily arise from radioactive material carried through (or by) them by the blood or deposited in them by blood.

No human data is available on genetic effects of high LET radiation, except possibly that from Kerala (Ko76), if it be assumed that the reported increase in Down's syndrome is due to internal alpha radiation: workers in Brazil (Ri75) find evidence that chromosome aberrations are due to high LET radiation from monazite sands, while there is no evidence of higher Down's syndrome in children of atom bomb survivors who were exposed to mainly low LET radiation (Sc62).

Experiments have been carried out in which ^{239}Pu has been injected into mice, and data collected on the induction of dominant lethals. Doses between 0.05 and 0.5 μCi per mouse increased the number of intra-uterine deaths if the Pu were in the form of citrate (from 9% to 12%), though as nitrate no significant effects were noted (Lu76, Lu76a). In an experiment with 0.1 μCi per mouse (Se76), only a non-significant (4.6%) increase on the frequency of induced dominant lethality was found. These data also indicated that the 0.1 μCi, or 4 μCi/kg body weight, gave a dose rate to the testes of 0.09 rads/day.

Genetic effects in humans as a result of inhalation or ingestion of alpha emitters depends on the uptake of the material to blood and then either to its deposition in the gonads or to the fraction of the blood in the gonads at any time. Taking Pu as an example, the maximum permissible amount in the total body may be taken as 0.03 μCi (ALI $\times f_1 \times$ 50 yrs). On the assumption that all this were in blood, then the specific activity would be 4×10^{-4} μCi in blood/kg body weight; however, as 90% of Pu in the blood is deposited in liver and bone (ICRP79) the actual figure should be an order of magnitude less. Taking 4×10^{-5} μCi/kg, and on the basis of the mouse data above, this could give a dose to the testes of 0.3 millirads/yr, which over a generation time of 30 years would produce a cumulative dose of 9 mrad. Taking Q=20, this is 0.2% of the generally accepted estimate of about 100 rem for the dose per generation for doubling the mutation rate.

Using parameters appropriate for inhaled (rather than injected) reactor plutonium, Cohen (Co 77a) has calculated that, over 30 years, 7 rem is given to the male gonads for every microgram of Pu inhaled (or, using Q=20, 14 rem/μg). From this, and using a genetic risk of 150 $\times 10^{-6}$ eventual genetic defects per man-rem, he estimates one (or two, with Q=20) eventual genetic defects per milligram inhaled in insoluble form (or, better, per milligram-man) or 2.6 (ICRP79) if the Pu is in insoluble form. The annual limit on intake of inhaled plutonium-239 is 200 or 500 Bq (class W or class Y), that is 0.1 micrograms, or class Y, 0.25 μg. It is appreciated that reactor plutonium has a slightly different activity/gram, but the calculation indicates that in the decade

20-30 years a worker should not receive a plutonium intake via inhalation sufficient to cause any significant genetic effect (less than 1 in a thousand).

6.3 Findings for External Neutron Irradiation

Table 6.3 summarizes in subjective terms the 12 studies we have seen on the effects of neutron radiation. These studies were undertaken for a variety of objectives, some only peripherally related to our mandate, so we have not attempted a quantitative synthesis of the data as was done for alpha emitters. The first listed (No59) compares two energy ranges of neutrons with x-rays but uses only a single dose and thus provides no insight into dose-response. None of the other seven studies show any evidence of concavity, though several show some degree of convexity, a few quite marked (notably Sh74, Mo77, St79 and Ul76). The shape of the dose response curve appears to be influenced by a number of factors including species of animal, dose range, dose rate, energy level, and site of tumor, but we have so far been unable to find any consistent pattern to these deviations from linearity. In any event, it is probably impossible to determine from these data whether the convexity is merely due to cell killing or is in fact a low dose phenomenon.

TABLE 6.1

ANIMAL STUDIES OF LUNG CANCER

Study Group	Dose	Number of animals		Cumulative Incidence		10^4RRI[1]
		at risk	lung cancer	crude	transformed[1]	
Inhaled Radon daughters (WLM) in rats (Ch76)						
"group A"	~400	26	2	.077	.080	2.0
"group B"	750	20	4	.200	.223	3.0
	1500	20	5	.250	.288	1.9
	3000	40	17	.425	.553	1.8
	4500	40	26	.650	1.050	2.3
	9600	40	30	.750	1.386	1.4
"group C"	2000	25	7	.280	.329	1.6
	3500	25	9	.360	.446	1.3
	5500	25	7	.280	.329	0.6
	7000	25	8	.320	.386	0.6
Intratrachael instillation of polonium-210 (cumulative rads at death) in hampsters (Li75)						
with ferric oxide adsorption	15	83	9	.108	.115	76.5
	75	82	10	.122	.130	17.3
	300	32	7	.531	.758	25.3
without ferric oxide adsorption	55	101	18	.178	.196	35.7
	1500	38	23	.605	.930	6.2
Inhaled plutonium-238 (cumulative rads 2 yrs after exposure) in rats (Sa73)						
"controls"	0	92	1	.011	.000	—
"group 1"	9	30	2	.067	.058	64.5
"group 2"	32	30	6	.200	.212	66.3
"group 3"	375	32	8	.250	.277	7.4
Intratracheal installation of Neptunium-237 (cumulative rads at death) in rats (Le72)						
controls	0	?	?	.036	.000	—
nitrate	5	50	8	.160	.138	275.4
	28	44	9	.205	.192	68.6
	138	48	6	.125	.097	7.0
	2500	49	7	.143	.117	0.5
oxalate	27	85	9	.106	.075	27.9
	134	89	8	.090	.058	4.3
	671	89	25	.281	.293	4.4
	3220	81	31	.383	.446	
Inhaled Polonium-210 (cumulative rads 280 days after exposure) in rats (Yu67)						
	0	147	0	.000	.000	—
	71	132	4	.003	.031	4.3
	202	129	13	.101	.106	5.3
	538	119	15	.126	.135	2.5
Inhaled injection of Plutonium-239 (cumulative rads at sacrifice) in BAF_1 mice (Te59)						
	115	21	1	.095	.000200[2]	1.74×10^{-6}
	2300	17	2	.118	.000313[2]	0.14×10^{-6}

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[1] RRI = $(R-R_0)/D$ where R = ln(1-CI) is the "transformed cumulative incidence" and Cl is the "crude cumulative incidence" and R_o is the transformed cumulative incidence in the control group, if provided.

[2] Rate per days at risk, taking R/T where T=500 days for the 115 rad group and 400 days for the 2800 rad group.

TABLE 6.2

ANIMAL STUDIES OF BONE SARCOMAS

Nuclide Animal (Reference)	Cell Killing Model Fitted to the Entire Dose Range: Dose Range (rads)	Number of Animals: At risk	Number of Animals: Sarcomas	Fitted Coefficients[1]: a	b	d_1	d_2	Chi Square (d.f.)	Test of Fit at Lower Doses: Dose Range (rads)	Number of Animals: At risk	Number of Animals: Sarcomas	Predicted	Chi Square (1 d.f.)
^{226}Ra beagles	147-10,900	74	38	.000	1.32	.0560	.0115	4.85 (3)	147-458	26	1	3.61	1.43
(Ma72a)									147-837	39	6	8.21	0.45
^{228}Ra' beagles	79-2896	59	26	.000	4.38	.5928	0	5.60 (5)	79-226	22	0	2.82	2.19
(Ma72b)									79-485	32	5	7.30	0.58
^{228}Th beagles	16-2870	79	38	.000	27.12	0	4.74	6.45 (6)	16-130	37	2	6.21	2.66
(Ma72c)									16-249	50	12	13.46	0.09
^{239}Pu beagles	78-4930	73	54	.000	21.06	.363	.320	0.11 (3)	78	14	4	3.92	0.06
(Ma72d)									78-191	28	13	12.70	0.01
^{226}Ra female CFI mice	26-28,900	2653	510	.012	.236	.0375	0	20.92 (11)	26-109	753	35	31.22	0.36
(F169a)									26-480	2179	265	247.94	1.25
^{239}Pu female CFI mice	10-1220	481	64	.011	.297	0	.00904	11.19 (7)	10-83	359	10	19.21	4.17*
(F162)									10-390	427	29	38.02	2.10
^{224}Ra female NMRI mice	30-6000	1416	115	.013	.0347	.0655	0	26.84 (8)***	30	200	16	8.93	5.07*
(Go71a)									30-150	548	58	44.67	4.01*
^{224}Ra male NMRI mice	150-6000	1161	35	.000	.00432	.0107	.000223	0.78 (5)	150	148	4	2.99	0.09
(Go71b)									150-750	444	18	18.78	0.00
^{239}Pu Wistar rats	1-76	2031	30	.000	(.00063[2] (.00143 (.00075	0	0	13.77 (7)†	1-20	485	4	3.99	0.06
(Bu70)									1-33	676	13	8.23	2.24
^{224}Ra female NMRI mice	30-1500	867	101	.013	.0371	.0626	0	12.81 (6)*	30-75	400	35	26.98	2.25
(Mu78a)									20-300	583	63	57.08	0.57
^{224}Ra male NMRI mice	150-1500	382	18	.000	.00379	0	.000412	0.12 (2)	150	97	2	1.80	0.05
(Mu78b)									150-300	195	5	5.30	0.01
^{227}Th female NMRI mice	20-10,000	700	245	.010	.140	.0485	0	50.68 (5)***	20-100	300	34	23.24	4.91*
(Mu78c)									20-1000	400	94	66.05	13.66***
^{237}Np Wistar rats	1-520	920[4]	109[4]	.000	.375[3]	.238	0	15.48 (14)	1-5	222[4]	5	1.63	5.09*
(Le72)									1-23	455[4]	11	11.01	0.02

Notes:

[1] Exposures expressed in units of injected dose (µCi/kg).

[2] Slopes for citrate inhalation, ammonium pentocarbonate inhalation, and oral citrate respectively (average skeletal dose in rads).

[3] Slope for intravenous administration of nitrate in males where dose is in rads: for intratracheal administration, multiply by 0.46; for oxylate, by 0.59; for females, by 1.92 (see text).

[4] Numbers surviving the minimum latent period estimated from the percentages given.

†P<.10 *P<.05 **P<.01 ***P<.001

TABLE 6.3

EXPERIMENTAL STUDIES OF NEUTRON IRRADIATION

Reference	Animal	Radiaiton Characteristics	Outcomes	Conclusions
No59	(C57LXA)F$_1$ mice	single whole body dose 288 MeV 290-580 rads	Solid tumors (GI,ovary,lung, etc) Nephrosclerosis	No comparisons in relation to dose possible
Da67	female RF/Un mice	single dose 1-2 rads/min 14 MeV 50-400 rads	thyemic lymphoma, myeloid leukemia, ovarian tumors	Dose-related but no clear characterization of shape
			life shortening	Slightly convex relation
			haematology, weight changes, lens opacities	Dose-related
Ba67	mouse spermatagonia	0.7 MeV 188 rads - 57 rad/min 62 rads - .001 rad/min	chromosomal abnormalities	Single dose-level only
Hu69	rabbits	0.7 MeV 2500 rads/hr 200-600 rads	osteosarcoma fibrosarcoma basal-cell carcinoma	Dose-related, but number of animals (25 total) insufficient to describe shape
Vo69 Vo72 Vo74	female Sprague-Dawley rats	single whole-body dose "fission" neutrons 2-20 rads	mammary tumors	Apparently high rates at 2-20 rads but several studies are combined and possibly misleading
Up70	female RF mice	1-5 MeV acute,85 rad/min chronic,10^{-6}-10^{-3}rad/min	myeloid leukemia thymic lymphoma	Dose-related but no clear shape
Sh74	female Sprague-Dawley rats	.43 MeV 0.1-6.4 rads	mammary tumors	Both studies show slightly convex relations with fitted exponents about .85. Neither linear nor square root models can be rejected.
Mo77	female Sprague-Dawley rats	35 MeV 0-40 rads	mammary tumors	
L176	human lymphocytes	0.7 to 14.6 MeV	chromosomal abnormalities	Low energy: linear High energy: linear-quadratic
U176	RFM mice	"fission" neutrons acute, 5&25 rads/min chronic, 1 rad/day	thymic lymphoma	Chronic: linear relation Acute: square-root relation
		0-200 rads	solid tumors (lung, ovary, pituitary & Halderean)	Dose related but no consistent shapes
U177	BALB/c mice	same as above	solid tumors (lung, mammary, ovary)	Dose-related but no consistent shapes.
St79	RFM and BALB/c mice	same as above	non-specific life-shortening	Linear or convex dose relations. High dose rate: greater convexity. Linearity better at <50 rads particularly for RFM mice.

FIGURE 6.1

FIT OF CELL KILLING MODEL TO ANIMAL STUDIES OF BONE SARCOMA

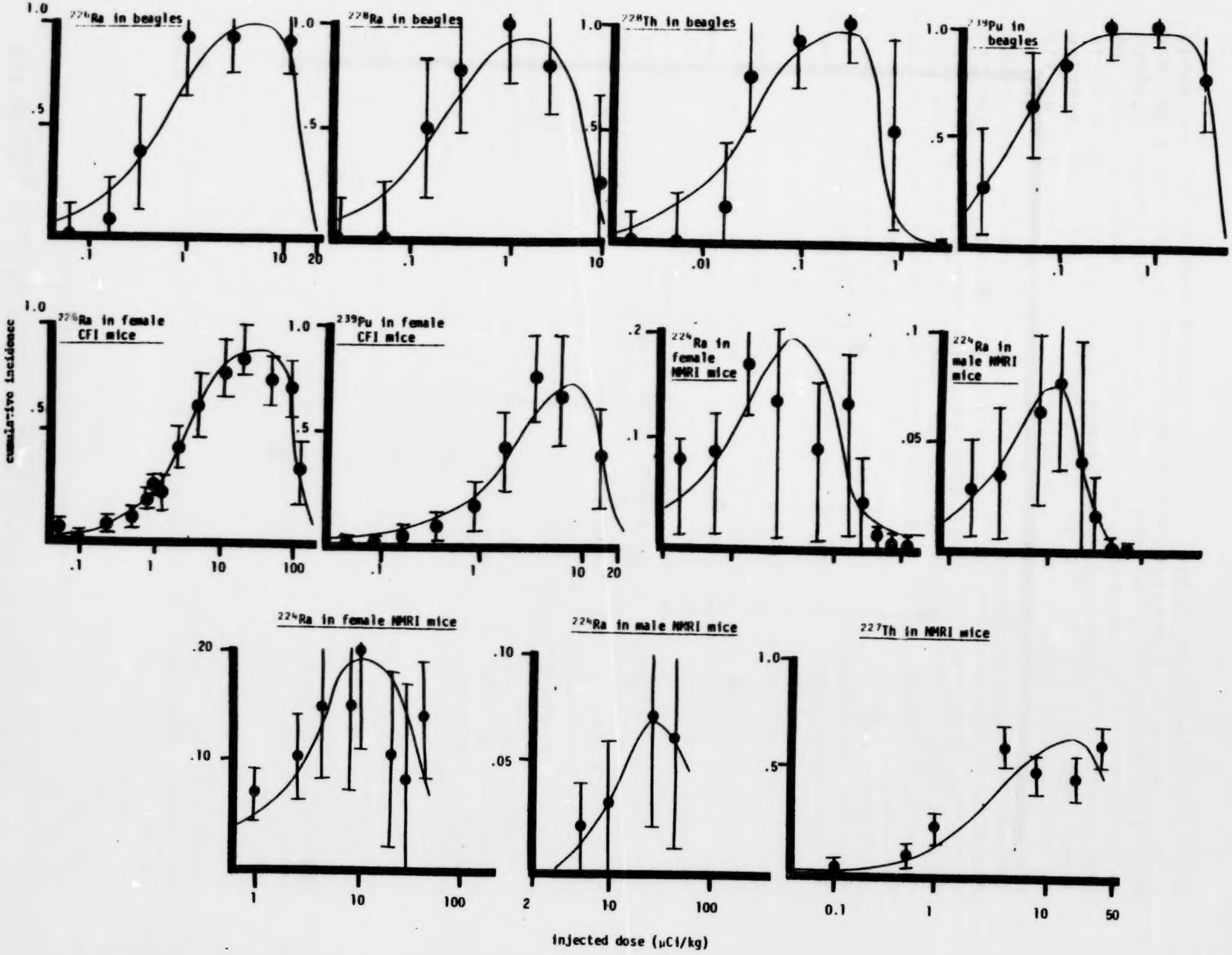
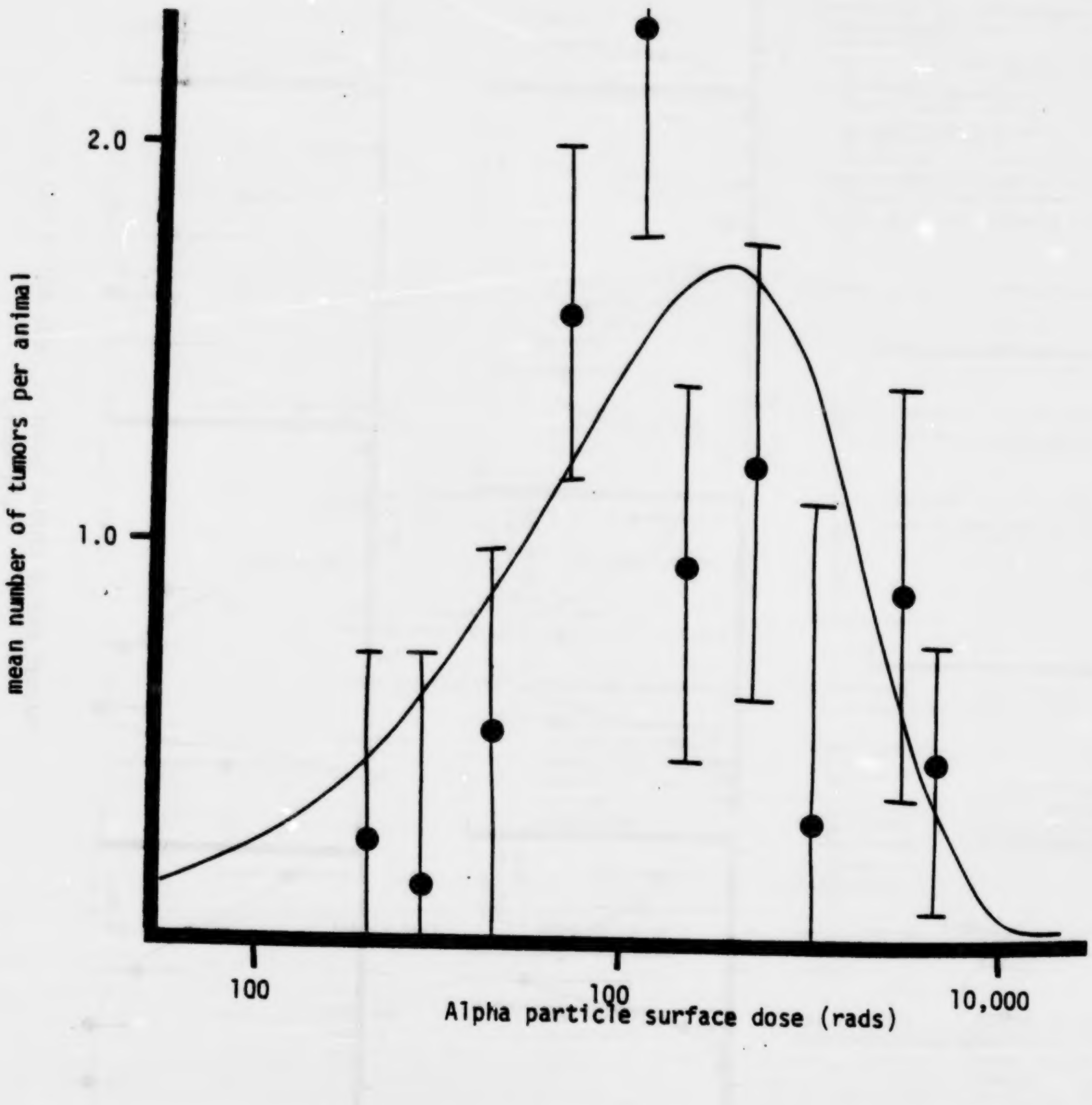


FIGURE 6.2

FIT OF CELL KILLING MODEL TO SKIN TUMORS IN MALE CD RATS
(Bu 68)



CHAPTER 7

CONFOUNDING AND MODIFYING FACTORS

7.1 DEFINITIONS

In this chapter, we discuss various factors (age, dose fractionation, smoking, other carcinogens, breathing rates, attachment to dust particles, etc.) which might require qualification of statements about relationships between radiation and risks. For each factor, either or both of two kinds of qualification may be required: confounding and effective modification (Mi74). As the two are frequently confused, it is worth digressing briefly to clarify the distinction. Confounding or modifying factors can be defined only in relation to an association between two other variables, typically between an "exposure" and a "disease" variable.

A variable confounds a relationship if it is associated with the exposure variable and if, even after accounting for the effect of exposure, it has an additional direct effect on the disease variable. By virtue of its joint relation to both exposure and disease, a confounding variable can induce an apparent association between the two even when no causal relationship exists, or it can cause a real association to be over- or underestimated. For example, Figure 7.1a illustrates a hypothetical dependence of risk on exposure in two subgroups of confounding factor, F. Since the subgroup F+ has larger exposures than F- and also shows higher risks, the crude dose-response relation (ignoring F) shows a spuriously steeper slope than either of the subgroups, whereas the adjusted relation shows the same slope. The effects of such confounding variables must be eliminated either by design or analysis for valid interpretation to be possible.

On the other hand, if the strength of the association between exposure and disease varies at different levels of a third variable, the latter is called an effect modifier. This phenomenon is illustrated in Figure 7.1b. A variable can be a confounder without being a modifier, or vice versa, or it can be both (Figure 7.1c). However, it is important to note that any statement about effect modification is meaningless unless the scale on which association is measured is stated. For example, suppose a modifying factor F acts by adding a constant additional risk to that caused by exposure to dose D (Figure 7.2a). Then on an attributable risk scale, the effect of F is a constant at all doses (and hence F is not an effect modifier) but on a relative risk scale, the effect of F decreases with dose (and hence it is a modifier). Conversely, if a modifying factor F acts by multiplying the risk at dose D by a constant factor (Figure 7.2b), then F is a modifier on an attributable risk scale but not on a relative risk scale. To avoid this ambiguity, we shall speak in terms of additive, multiplicative, or other models on a scale of absolute risk.

7.2 TEMPORAL FACTORS:

Under this heading, we consider all factors involving time: age at exposure, age at risk, duration of exposure and dose rate, time since exposure (latency), pattern of exposure, etc. As risk itself is defined in relation to time intervals (Section 4.1), it is clear that the analysis of such factors is considerably more complex than other kinds of variables considered in later sections and an appropriate method of cohort analysis is essential to avoid confounding, especially in view of the close relationship of all these factors to the principal exposure variable, total dose. Finally, as these various factors are strongly interrelated, their effects can be difficult to interpret unless considered simultaneously, which is rarely done. In the sections which follow, we have tried to indicate the limitations to the validity of the reported findings, but in lieu of more rigorous analyses, we have generally accepted the various findings at face value.

7.2.1 Age at exposure and age at risk

7.2.1.1 Lung cancer. Table 7.1 summarizes the data available from eight studies on the modifying role of age on radiation effects. These data are of fundamental importance in choosing between the attributable and relative risk models for projecting risk estimates beyond the end of follow-up (Sections 4.2.2 and 8.2 and Appendices L and M). Before describing each set of results separately, it is important to note that studies differ both in the definition of the modifying factor (age at exposure or at risk) and in the parameters of effect used (attributable or relative risks, total or per unit dose).

For the Colorado plateau uranium miners, no age breakdown of the latest mortality data is available, so the figures in Table 7.1 come from the results of follow-up to 1968 (Lu79, as quoted in our Table K.2b, based on only 62 lung cancer deaths compared with 159 in the latest report). Attributable and relative risks are quoted per unit of "effective" exposure assuming a log-normal distribution of latent periods with a median of 10 years. While this is a very sensible index to use for this purpose, it could be misleading for describing how projections based on a simple accumulation of exposure (ignoring latency) would perform. The results suggest that the interaction of age with "effective" dose is intermediate between additive and multiplicative models in these data. Table 7.2 describes the results of fitting the attributable and excessl relative risks to the nonlinear model used in Chapter 5 with an additional factor for the age dependence, i.e. AR or RR-1 = bD^cA^d where D is effective exposure WLMs and A is age at risk. The data for this fitting come from separate breakdowns of dose (Lu71) and age effects (Lu79), combined as desccribed in Appendix K.2.2; this combination is somewhat crude but, given the data available, seems to be the best way of obtaining risk indices for projection purposes (Section 8.2.1.2). The data clearly confirm the increase in attributable risks and the decrease in relative risks with age apparent in Table 7.1., and also support the convexity noted for the simple cumulative exposure in Tables 5.2 and 5.3.

The Czechoslovakian data show a similar increase in attributable risks per WLM (per person, not person-years) with increasing age at first exposure, but the data reported do not allow relative risks to be estimated. The results reported here encompass only the low exposure groups. Above 300 WLM, the slope of the dose-response relation appears to decrease with increasing age, which may be an artefact of the incorrect method of analysis used (Section 5.1.1.1).

Both the Ontario and Newfoundland data show relative risks increasing markedly with age at first exposure. Though absolute risks are not available, they would surely be increasing even faster with age. These risks are not quoted per unit of exposure, but it seems unlikely that the miners who started at older ages would have accumulated substantially more exposure than the younger ones; indeed, one would expect the reverse. Nevertheless in the Ontario cohort, the lung cancer cases who were older at start had in fact accumulated 30% more exposure, but this is insufficient to explain their much higher relative risk. We have made no adjustments for latency in the Czech, Newfoundland, or Ontario figures because the rate of expected deaths in the comparison groups would certainly vary with age in an unquantifiable manner.

The studies of three Swedish metal mining populations allow estimates of relative risk, but not in relation to exposure. These relative risks are either virtually constant, or in the case of Malmberget strongly increasing, but as the modifying variable is age at risk rather than age at first exposure, it is less likely that the groups compared would have similar exposures. However, it is clear that attributable risks would have to be very strongly increasing with age, and probably would still be increasing even if expressed per unit of exposure.

Of all the studies, the atomic bomb survivors show the strongest trend of increasing effects with increasing age. As the exposure was at a single instant, the distinction between age at exposure and age at risk becomes much less important here. Attributable risks per rem show a more than 100-fold increase with age while even relative risks per rem show a 10-fold variation.

In summary, all eight studies of lung cancer show or imply attributable risks per unit dose strongly increasing with age whereas relative risks are more stable, decreasing in some, increasing in others, but never to as large an extent as attributable risks. The implication of this is that for lung cancer, use of the attributable risk projection model is likely to grossly underestimate the lung cancer effect of radiation over an entire lifetime, unless the risk indices are allowed to vary with age.

7.2.1.2 Other tumors. Table 7.3 summarizes the epidemiological evidence for age effects on other sites. For both of the radium-exposed populations, effectiveness appears to be greater in children than in adults, probably reflecting their larger bone doses per unit of activity received. (For the dial painters, the explanation does not appear to be that those younger at first exposure had higher systemic intake; among the subgroup measured, the younger had lower intakes, but this subgroup was too small to allow reliable inferences about effectiveness.) For the atomic bomb survivors, leukemia shows a U-shaped distribution with a minimum in the 35-49 year age at time of bombing (ATB) range; the attributable risk is somewhat more stable than the relative risk. For all other cancers (excluding leukemia and lung) attributable risks rise rapidly with age till 50 years but show no excess thereafter; relative risks are somewhat more stable than attributable risks.

7.2.2 Latent periods

7.2.2.1 Lung cancer. Before describing the effects of time since exposure, it will be helpful to introduce some terminology. The concept of a "latent period" as an interval between exposure and subsequent effect is not well defined in epidemiology, particularly when the exposure extends over a substantial period (Ro81). It is useful to define a biological latent period (BLP) as the interval between some increment of exposure and a later increase in risk which is attributable to it. This BLP is not generally a fixed quantity, but a random variable having some distribution (Kn73). However, as this distribution is not easily estimable from cohort studies, epidemiologists have tended to work instead with a proxy measure which we shall call the epidemiologic latent period (ELP), the interval between first exposure and death among those who have died prior to the end of follow-up (Ar73b). It is important to realize that the distributions of ELPs and BLPs may bear little relation to each other because (1) the ELP is measured from the first rather than average exposure time, (2) the ELP distribution may miss many cases that have not yet appeared, and (3) the ELP distribution may include many cases which were not attributable to the exposure factor under study. A detailed discussion of the potential for misleading conclusions about effects of dose on latency and vice versa is provided in Appendix M.

Two types of questions are relevant in this context. First, what is the distribution of latent periods (ELPs or BLPs) and do they depend on dose? And second, how should this information be used to construct a meaningful index of cumulative exposure for long-term exposures? Unfortunately, these two questions are so deeply intertwined that unscrambling them can become an exercise in circular reasoning (Th81b).

The data on the atomic bomb survivors are particularly useful for describing latent period effects because the exposure was instantaneous. Table 7.4 describes attributable and relative risks among those exposed to 10 or more rads kerma compared with the 0-9 rad group, in relation to time since exposure. By either index, lung cancer risks began to increase 10-13 years after exposure, reaching a peak 14-17 years after and gradually declining thereafter, with an excess still apparent nearly 30 years after. This distribution may be somewhat biased if the standard of diagnosis has changed over this period, particularly as knowledge of the radiogenic cause of this cancer became better known in the late 1960s.

Of all the mining populations exposed to radon daughters, the Colorado plateau study provides the best data on latency. Unfortunately, these too are available only on the follow-up through 1968 and are thus seriously limited both in terms of numbers and length of follow-up. However, latent periods have been described in two ways. First, Table 7.5 (taken from Ar73b, Table 2) describes relative risks as a function of time since first exposure. Since the measure is an increase in risk, this is closer in spirit to the biological latent period, even though the intervals are described in relation to first exposure rather than each increment of exposure. Obviously, as this interval increases, so does cumulative exposure, but we see a clear increase in excess relative risks per unit dose up to 15-19 years and a decline thereafter (somewhat larger on a relative than on an attributable risk scale). This decline is not simply a reflection of censoring of observation by close of follow-up (as with ELPs) because observed and expected deaths should be equally censored.

In a second approach, the investigators attempted to estimate the parameters of a log normal distribution of ELPs by constructing an index of "effective" exposure, defined as the sum over all exposure increments of the dose rate times the log normal probability associated with the interval from the exposure instant to the instant at risk (Appendix M). The parameters were then chosen by trial and error, where the fit was judged by the agreement of observed with predicted cases for calendar year, age at death, smoking, and other breakdowns (Lu71, Lu79). By these criteria, a median of 10 years with a dispersion factor of 1.5 was found to fit best. This is a shorter median than suggested by Table 7.5, probably because the effective WLM is defined in terms of time intervals since each increment of exposure rather than since the first exposure. Using this model, no effects of age at first exposure (adjusted for age at risk) or of average dose rate (adjusted for cumulative dose) on risk were apparent and no effect of cumulative dose on latent period was observed.

The only other study of mining groups which provides data on latency is that of the Newfoundland fluorspar miners (dV80). The authors provide distributions of ELPs in three subgroups by year of first employment (Figure 7.3). The earliest subcohort would have been followed for 30 to 39 years from first employment so although a decline in deaths is apparent starting 25 years after first employment, the magnitude of the decline is doubtlessly exaggerated. For later sub-cohorts, the ELP distribution becomes increasingly less meaningful. Regression analyses failed to find any relation between ELPs and age at first exposure or average dose rate, but these results are largely uninterpretable due to the complicated way these factors would relate to the censoring pattern (cf. Appendix M).

7.2.2.2 Other tumors. Table 7.4 also describes BLPs for other cancers among the atomic bomb survivors. Depending on the risk index used, leukemia risks peaked either 5-9 or 14-17 years after exposure and have uniformly declined since, being close to expected at 30 years after exposure. On the other hand, all other cancers (except lung) show a uniform excess by either index except for an isolated shortfall 10-13 years after exposure. Thus it is likely that excesses for some sites will continue to appear for some time.

Bone sarcomas among the ^{224}Ra-injected patients (Ma78) had relatively short latent periods, ranging from 3.5 to 22 years (modes 6-8, mean 10). As the effect is nearly completely expressed by now and entirely attributable to exposure (which was short for most subjects in relation to the latent period), the distribution can be studied in relation to dose with less concern about censoring effects. The mean latent period shows a decline of about 1 year per 1000 rads. For the radium dial painters (Ro78a), bone sarcomas had much longer latent periods, ranging from 7 to 52 years (mean 27) and head carcinomas even longer (range 19 to 52, mean 39); more tumors may yet appear with longer follow-up. It is quite plausible that these longer latent periods are due to the longer half-lives of the isotopes. Evans (Ev74) has claimed to find a similar reduction in latency with increasing dose and accordingly postulated a "practical threshold" dose, below which the latent period would exceed the life expectancy. However, his claim is not well supported by the data, particularly in view of the censoring bias discussed earlier. Furthermore, by fitting an inverse power function rather than a linear relation between dose and ELPs, he loads the dice in favor of his hypothesis, as the predicted ELP would necessarily diverge to infinity at zero doses.

Several animal studies also show a shortening of ELPs with increasing dose, notably for bone sarcomas (Ma72, Fi69, Mu78) and neoplasms induced by neutrons (Up70). However, all of these findings are likely to have been heavily influenced by the very high death rates which led to much shorter mean survival times at these very high doses (e.g. St78).

7.2.3 Protraction and pattern of exposure

Figure 7.4 summarizes the results of eight studies of the effects of varying dose rates and durations of exposure.

7.2.3.1 Lung cancer. Only the Czechoslovakian study (Ku79) provides any epidemiological evidence on the effect of protraction of exposure. Within broad categories of cumulative exposure, attributable risks increased with increasing duration of exposure, dramatically so in the higher dose categories. Similarly, within three out of four cumulative exposure categories, risks were highest among those with decreasing patterns of exposure and lowest among those with increasing patterns (as would be expected in the presence of latency). However, these results must be interpreted with some caution, first as the cumulative exposure may not be comparable across the categories being compared, and more importantly because an inappropriate method of cohort analysis had been used to estimate these rates (Section 5.1.1.1); the bias in this method of analysis would affect the long-duration and increasing pattern groups more heavily than the others, possibly accounting for the observed effects.

In a study of rats exposed to radon and its daughters (Ch76), a similar effect of protraction was observed. "Group A" (see Table 6.1) was chronically exposed to low concentrations of pure radon (which were assured to be in equilibrium with 30% daughters) for 5-hour daily sessions, and produced the highest effectiveness (19 cancers/10^5 WLM-rat). "Group B" was chronically exposed to high concentrations of radon and its daughters for 5 hour daily sessions and produced lower effectiveness (11 cancers/10^5 WLM-rat). "Group C" was more acutely exposed to high concentrations for 16 hour daily sessions, and produced the lowest effectiveness (7 cancers/10^5 WLM-rat).

7.2.3.2 Bone sarcomas. A similar direct relation between duration and effectiveness (or equivalently, an inverse relation between dose rate and effectiveness) at the same total dose has been reported for bone sarcomas induced by the short-lived ^{224}Ra, both among the radium-injected patients (ma78) and mice (Mu78). Both sets of data fit well to a relation of the form $R = bD[1 + c(1-e^{-fT})]$ where D is the total average skeletal dose and T is the duration of exposure.

7.2.3.3 Other effects. Five experimental studies using neutron irradiation at varying dose rates have reported similar findings for a variety of endpoints, each finding that the effect of protraction was the reverse of what is generally observed for low-LET radiation (where protraction tends to decrease effectiveness). These included one study of chromosome aberrations (Ba67), three of various neoplasms (Up70, Ul76, Ul77) and one of nonspecific life shortening (St79). As noted in Section 6.3, the general findings were that acute high dose-rates tended to produce convex relations whereas chronic low dose-rates produced linear relations. As a corollary, at low total doses acute exposures were more effective whereas at high total doses chronic exposures were more effective, though there was some variation in these findings from site to site (see Table 6.3).

7.3 SMOKING AND LUNG CANCER INTERACTIONS

As smoking is the single largest determinant of lung cancer rates, no study of lung cancer is complete without some discussion of its possible confounding role. To diagnose confounding, one must determine whether the exposed cohort had different smoking habits than the comparison population or whether smoking and amount of exposure were associated. For example, among the Czechoslovakian uranium miners, a separate survey of a random sample of miners found no differences in smoking habits from the general population, so a confounding role could be ruled out. On the other hand, the Newfoundland fluorspar miners are known to have had an unusually high prevalence of smoking, so relative risks based on Newfoundland rates are considerably exaggerated. However, only for the Colorado plateau miners and the atom bomb survivors are both smoking and radiation exposures available on the same individuals, thereby allowing estimates of radiation effects to be adjusted for smoking and permitting study of the interaction between the two effects. For neither set are there substantial differences between the crude and the smoking-adjusted effects, so we have no reason to change our conclusions in Chapter 5 about *average* slopes of dose-response relations.

Table 7.6 summarizes the results of all studies which might shed light on effect modification by smoking. For the Colorado plateau, two versions of the data are available. Both relate to the period 1950 to 1974, but the more recent (Ar78a) includes an additional 31 deaths originally classified to other respiratory causes. The more recent is also broken down by years after start of uranium mining, and we have restricted our analyses of this data set to the period 10 or more years after follow-up; respiratory cancer deaths in this period (after reclassification) total 159. The earlier version (Ar76) is not broken down by time since start and includes 12 deaths 5-9 years after start, for a total of 144 (before reclassification). Expected deaths for both data sets are based on the distribution of person-years, scaled so that the total observed and expected deaths are equal; thus, neither set is adjusted for age or calendar year, which certainly would confound inferences about the main effects of smoking and radiation, and might also confound inferences about their interaction. In the more recent version, the person-years are not provided and have had to be calculated from the numbers of deaths and rates per 1000 PY which are provided; in the subgroups with zero deaths, the person-years have had to be estimated, as described in Appendix K.2.2, which adds to the uncertainty in these data. For both data sets, we have grouped the never, former and light (less than 20 cigarettes per day) and the moderate and heavy (20+ cigs/day) smoking categories and the radiation categories as indicated for ease of presentation and have expressed risks relative to the lowest category of both factors. The full details of their original tabulations are presented in Figure 7.5, with risks and 95% confidence intervals expressed relative to the entire group, plotted on a logarithmic scale. The regrouped data suggest a greater than multiplicative interaction, as the joint effect, RR 5.4 (respectively 5.7) is greater than the product of each effect alone, 2.4 × 2.0 = 4.8 (respectively 4.1). To some extent this conclusion is an artefact of the choice of categories, and fitting a general model of the form

$$RR_{ij} = \alpha(1 + \beta_i + \gamma_j + \delta\beta_i\gamma_j) \qquad [7.1]$$

where i denotes the smoking category, j the radiation category and α, β_i, γ_j, and δ are parameters to be estimated, allows tests of the goodness of fit of the various models to be performed (Table 7.6). By constraining the "mixture parameter" δ to 0 we get a simple additive model whereas $\delta = 1$ produces a simple multiplicative model, and allowing it to be free provides a broad range of alternatives including antagonism ($\delta<0$), synergy ($\delta>1$) and intermediate possibilities (Th81a). For the Colorado data, the multiplicative model fits much better to both versions of the data, the tests against the mixture model in both cases rejecting the additive model ($\chi_1^2 = 15.02 - 3.41 = 11.61$, $p<0.001$ or $13.90-4.33 = 9.57$, $p<0.01$). This impression is confirmed by inspection of the fitted curves in Figure 7.5.

The atomic bomb survivors show somewhat different results. For the broad grouping of smokers and nonsmokers, relative risks adjusted for age and sex fit well to an additive model, the RR for the joint effect being 8.6 which is only slightly larger than predicted by the additive model 6.2 + 3.0 - 1 = 8.2. A finer breakdown of smoking habits (not adjusted for age or sex) is provided in Figure 7.6 and the resulting fits of the model [7.1] are described in Table 7.7. The better fit of the additive model is confirmed, but the data would also be consistent with a multiplicative model. The reason is apparent from the width of the confidence intervals for the 200+ rad group, which are based on very small numbers of subjects. An additional uncertainty is that a large proportion of the smoking histories (mainly among low dose controls) are estimated rather than observed.

For the Czechoslovakian miners, no individual smoking histories are available except for the lung cancer cases. Based on certain assumptions about the smoking distribution, the relative risk for smoking, and the comparability of their ages, the expected numbers of cases among smokers and nonsmokers quoted in Table 7.6 have been estimated (BEIR80), suggesting similar relative risks for radiation in both groups, i.e. a multiplicative model. However both the smallness of the number of nonsmokers and the validity of the assumptions means little credence can be put on these conclusions.

Two Swedish metal mining studies provide data on smoking, but only amongst miners with no comparisons of radiation effects (i.e. effect modification) possible. The Zinkgruven data appear to suggest a protective effect of smoking, which is quite implausible; their attempt to adjust for other factors is nonsense as they include the exposure variable smoking in their confounder score. The Malmberget data indicate a main effect of smoking, but say nothing about interactions with radiation.

In summary, it appears that the interaction between radiation and smoking may be intermediate between additive and multiplicative, though on balance we would favor the multiplicative model. This would be convenient in view of our preference for the relative risk model for age effects, as it means the relative risk model could also be used for projecting risks to settings with different smoking distributions (e.g. as a test for the consistency of low dose predictions with the "natural" incidence, cf. Section 8.3.1. However, it is worth mentioning that an additive model for smoking would not necessarily be inconsistent with a relative risk model for age as explored in Section 8.2.1.2. Indeed, under the presently favored "multistage model" for carcinogenesis (Pe77), this is precisely what would be predicted if radiation and smoking acted at the same stage.

The interaction between smoking and radiation has been looked at in another way. Instead of comparing risks, some authors have compared mean ages at death and epidemiologic latent periods between smokers and non-smokers (Colorado plateau, Ar73a; Zinkgruven, Ax78). Both authors found these parameters to be substantially shorter among smokers and concluded that smoking acts by promoting a radiation initiated cancer. These are potentially valuable approaches to the question, but require more rigorous approaches to the analysis to overcome the limitations of ELPs discussed above (Th81b and Appendix M).

In a study of rats exposed to radon daughters (Ch78), those additionally exposed to tobacco smoke showed a 32% cumulative incidence of lung cancer compared with 17% among those not exposed to tobacco smoke. As no lung cancer was found among those exposed only to smoke, a synergistic effect is apparent.

7.4 EXPOSURE OF MINERS TO DUST, DIESEL FUMES, AND OTHER AGENTS

Miners are likely to be exposed to other agents which may themselves be either carcinogenic or may modify the carcinogenic effect of radiation. Dust plays a special role here through the electrostatic attachment of radon daughters to it, as discussed in Section 7.5. However, no epidemiologic data appears to be available to describe the joint effects of such agents in combination with radiation. Animal studies indicate synergistic effects (i.e. interactions greater than additive) of ionizing or ultraviolet radiation with estrogens, haematite, cerium, methylcholonthrene, nitroquinoline, cortisone, urethane and dimethyl benzathracene; other substances have shown either no effect, simple additive effects or an antagonistic effect (Lu71).

7.5 BREATHING RATES

The rate of deposition of radon daughters depends on breathing rate (Appendix E.5). To a first approximation the intake of daughters will be linear with breathing rate. As the breathing rate might well vary with size cubed (mass) and area of deposition as size squared (area of bronchial surface) this might imply that effective dose would increase with size. On the other hand, among the Colorado plateau miners, risks of lung cancer and chronic respiratory insufficiency were found to decrease with height (Ar78a). The percentage retention of daughters may slightly depend on tidal volume with the percentage increasing with total volume (varying by ± 15%).

7.6 ATTACHED FRACTIONS

On the model that the free ions of RaA are responsible for much of the potential carcinogenic effects, the proportions of radon daughters (particularly RaA) which are attached or unattached to aerosols are of importance (Appendices E.3 and E.4). The greater the particulate concentration in the air, the less the unattached fraction; a rise of a factor of 3 or 4 in concentration would reduce this fraction by a factor of about 4. Aerosol size also affects the fraction. In modern mines a figure of 4 or 5% unattached seems reasonable, but there may be a range of values within a factor of 4.

In an attempt to test the hypothesis that a uniform distribution of radiation in the lung is less effective than a set of "hot particles", Litte *et al*. (Li78) injected ^{210}Po intratracheally into Syrian hamsters by two methods: dissolved in saline, and absorbed onto Fe_2O_3 particles. The latter yielded fewer tumors per unit dose, implying that a dose model based on a uniform distribution would not underestimate risks.

7.7 GENETIC MARKERS OF SUSCEPTIBILITY

The possibility that certain genetic strains are particularly radiosensitive is discussed in Appendix F.1 and Section 2.4.2. Such strains might also be characterized by an abnormal number of chromosome aberrations (unconnected with radiation effects). Such strains are known but constitute a very small number of persons in the general population (perhaps some thousandths of one percent). Moreover, on the relative risk model, which seems most appropriate for radiation problems, the relative risk of an irradiated group of persons with these genetic traits would be the same as that of any member of the general population.

7.8 RADIATION ENERGY

The shape of dose-response relations for chromosome abnormalities have been found to vary with the neutron energy of neutron irradiation (L176). Fitting each set of data to a linear-quadratic model, a pure linear model was found to fit best at 0.7 and 0.9 MeV, the quadratic term becoming increasingly important at energies of 7.6 and 14.6 MeV (though still contributing less than for pure gamma radiation). On the other hand, for breast tumors, 0.43 MeV and 35 MeV both showed convex dose-response relations with similar exponents ($\hat{c}$ = 0.85 and 0.86 respectively), but the low-energy neutrons produced an estimate of slope ($\hat{b}$ = 8.4) about 5-times higher than the high-energy neutrons ($\hat{b}$ = 1.6) (Mo77); this is probably because slopes were given in units of rads rather than rems.

TABLE 7.1

SUMMARY OF STUDIES OF RADIATION - AGE INTERACTIONS FOR LUNG CANCER

tudy	Age Category	Lung Cancer Cases		Risk Indices	
		Observed	Expected	Attributable	Relative
olorado plateau	Age at risk	All miners of region		10^6AR/PY-WLME	10^2(RR-1)/WLME
(Lu79)	35-54	30	5.34	35.6	8.62
	55-64	23	6.61	105.0	4.80
	65+	9	4.56	101.4	2.05
zechoslovakia	Age at first exposure	0-299 WLM cf.nation		10^2AR/WLM	
(Sv76a)	10-29	NA	NA	1.13	NA
	30-39	NA	NA	1.73	NA
	40+	NA	NA	2.43	NA
ewfoundland	Age at first exposure	all miners cf.surface			RR-1
(dV80)	10-19	19	6.46	NA	1.94
	20-34	33	7.22	NA	3.57
	35+	19	1.94	NA	8.78
ntario	Age at first exposure	31+WLM cf. 1-30 WLM			RR-1
(He76)	10-35	15	6.25	NA	1.40
	36+	36	9.20	NA	2.91
Sweden	Age at risk	all miners cf.region			RR-1
iruna Jo 73)	30-59	5	1.65	NA	2.03
	60-74	8	2.82	NA	1.82
almberget (Re74)	20-54	3	0.42	NA	7.1
	55-64	11	0.60	NA	18.3
inkgruven Ax78)	10-69	14	0.84	NA	15.7
	70+	7	0.44	NA	14.9
tomic bomb urvivors	Age at exposure	10+rad cf. 0-9 rad		10^6AR/PY-Rem	10^2(RR-1)/Rem
(Be78a)	10-34	11	10.1	0.04	0.13
	35-49	65	51.3	1.90	0.45
	50+	51	31.5	7.16	1.21

A Not available

TABLE 7.2

FIT OF LINEAR AND NON-LINEAR AGE-INTERACTION MODELS TO LOGNORMALLY WEIGHTED EFFECTIVE EXPOSURES (WLME) IN COLORADO PLATEAU URANIUM MINERS

Model	Estimates (s.e.) of parameters			Goodness of fit		
	b	c	d	Chi square	df	p
Attributable $AR = e^b D^c A^d$	-10.09 (0.19)	1.00	0.00	32.26	11	0.0007
	-23.12 (4.13)	1.00	3.40 (1.06)	19.28	10	0.037
	- 9.36 (0.92)	0.83 (0.22)	0.00	29.59	10	0.001
	-22.21 (4.01)	0.83 (0.18)	3.35 (1.00)	16.56	9	0.056
Relative $RR=1+e^b D^c A^D$	- 2.63 (0.19)	1.00	0.00	33.25	11	0.0005
	10.01 (0.22)	1.00	-3.23 (0.06)	17.82	10	0.058
	- 2.04 (0.24)	0.87 (0.05)	0.00	31.51	10	0.0005
	11.06 (0.34)	0.74 (0.31)	-3.20 (0.49)	13.80	9	0.130

TABLE 7.3

SUMMARY OF STUDIES OF RADIATION-AGE INTERACTIONS FOR OTHER CANCERS

Study	Age Category	Deaths		Risk Index	
		Observed	Expected	Attributable	Relative
Radium dial painters	Age at first exposure	Bone sarcomas			RR-1
Po78	≤19	19	8.22	NA	0.31
	20+	3	8.74	NA	<0
Radium-injections	Age at first injection	bone sarcomas		AR/10^5 person-rads	
Sp70	1-5	8	0	13.0	NR
	6-10	14	0	17.0	NR
	11-15	7	0	13.9	NR
	16-20	4	0	8.8	NR
	21+	10	0	6.9	NR
Atomic bomb survivors	Age at exposure	leukemias		AR/10^6 PY-rem	(RR-1)/10^2rem
(Be78a)	0-9	19	3.22	2.85	9.47
	10-19	19	2.52	1.77	8.67
	20-34	21	4.71	2.13	5.20
	35-49	18	10.92	0.98	1.11
	50+	13	3.00	3.67	6.53
		all except lung and leukemia			
	0-9	11	6.31	0.85	1.44
	10-19	43	37.99	0.54	0.17
	20-34	149	118.67	3.97	0.38
	35-49	493	441.97	7.07	0.20
	50+	408	412.27	<0	<0

TABLE 7.4

BIOLOGICAL LATENT PERIODS AMONG THE ATOMIC BOMB SURVIVORS

Time since exposure (yrs)	Deaths[1] Observed	Expected	Attributable Risk per 10^6PY	Excess Relative Risk
Lung Cancer				
5- 9	3	2.7	2.9	0.11
10-13	6	4.0	21.5	0.51
14-17	23	13.0	112.2	0.77
15-2	27	19.1	92.9	0.42
21-25	34	28.6	67.0	0.19
26-29	34	26.1	107.8	0.29
Leukemia				
5-9	27	4.7	22.3	4.77
10-13	19	5.6	13.4	3.41
14-17	18	2.6	15.4	5.86
15-20	12	3.0	9.0	3.00
21-25	9	4.5	4.5	1.00
26-29	5	3.5	1.5	0.44
All other cancers				
5-9	145	125.2	19.8	0.16
10-13	136	165.5	<0	<0
14-17	189	167.3	21.7	0.13
15-20	203	183.4	19.7	0.11
21-25	214	187.3	26.7	0.14
26-29	217	189.9	27.1	0.14

---

[1] Observed and expected deaths in the 10+ rad kerma group, using the 0-9 rad group as standard, Hiroshima and Nagasaki combined. (Source Bë78a)

TABLE 7.5

QUASI-BIOLOGICAL LATENT PERIODS[1] FOR LUNG CANCER AMONG THE COLORADO PLATEAU URANIUM MINERS

Time since First Exposure (yrs)	PY[2]	Lung Cancer Cases		Mean Exposure[3] (WLM)	10^6AR/PY-WLM	10^2(RR-1)/WLM
		Observed	Expected			
0- 4	9,433	2	1.41	370	0.17	0.11
5- 9	13,225	12	3.39	637	1.02	0.40
10-14	9,088	24	3.42	964	2.35	0.62
15-19	3,277	19	1.41	1640	3.27	0.76
20-24	1,501	6	0.74	2067	1.70	0.34
25+	1,433	7	1.34	2404	1.64	0.18

[1] Intervals from first exposure to a subsequent increase in risk (Source Ar73.).

[2] Taken from Appendix Table 39 of Lu71 which differs slightly from Ar73a in the marginal distribution by cumulative WLM category

[3] Average of the mid-points of 6 exposure categories, weighted by the distribution of person-years in each latent period category.

TABLE 7.6

SUMMARY OF STUDIES OF RADIATION-SMOKING INTERACTIONS FOR LUNG CANCER

Study	Smoking Category	Radiation Category	Lung Cancer Cases		Relative Risk[2]
			Observed	Expected[1]	
Colorado plateau (Ar78a)	Never,former and light	1-1799WLM	22	48.1[3]	1.0
		1800+WLM	20	18.2[3]	2.4
	heavy	1-1799WLM	65	71.8[3]	2.0
		1800+WLM	52	20.9[3]	5.4
Colorado plateau (Ar76)	Never, former and light	1-359WLM	9	28.4	1.0
		360+ WLM	29	34.3	2.7
	heavy	1-359 WLM	15	30.8	1.5
		360+ WLM	91	50.5	5.7
Czechoslovakia (Ho77)	Nonsmokers	All cf.population	5	1.0	5.0
	Smokers	All cf.population	110	23.5	4.7
Sweden:					
Zinkgruven (Ax78)	Nonsmokers	All miners	9	3.6	1.0
	Smokers	All miners	10	15.4	0.2
Malmberget (BEIR80)	Never	All miners	7	15.0	1.0
	former(15yr or more)	All miners	9	15.0	1.3
	current	All miners	29	15.0	4.1
Atomic bomb survivors (Is75)	Nonsmokers	<1 rad	11	36.3	1.0
	Smokers	<1 rad	50	30.9	6.2
	Nonsmokers	≥200 rad	4	3.1	3.0
	Smokers	≥200 rad	9	3.6	8.6

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[1] Based on distributions of person-years, subjects, or controls, scaled so that the total observed and expected are equal (except for Ho77, where expected cases are based on calculations in BEIR80).

[2] Ratios of (Obs/Exp), relative to the lowest smoking-radiation category.

[3] Expected deaths based on person-years estimated from deaths and rates 10 or more years after first employment, provided in Ar78, with person-years in cells where no deaths occurred estimated from the marginal distributions; see appendix K for details. Ar76 data requires no such estimation, but is based on many fewer deaths and includes deaths 5 or more years after first employment.

TABLE 7.7

FITS OF ADDITIVE AND MULTIPLICATIVE MODELS FOR EFFECTS OF RADIATION AND SMOKING ON LUNG CANCER

Study	Model	Mixture parameter (standard error)	Goodness of Fit		
			chi-square	df	P-Value
Colorado plateau[1] (Ar78a)	additive[2]	0.0	15.02	5	.01
	multiplicative	1.0	3.57	6	.73
	mixture	1.38 (3.80)	3.41	5	.64
Colorado plateau (Ar76)	Additive	0.0	13.90	8	.08
	multiplicative	1.0	4.58	8	.80
	mixture	0.46 (.56)	4.33	7	.74
Atomic bomb (Is75)	additive	0.0	1.57	3	.67
	multiplicative	1.0	3.92	3	.27
	mixture	-0.05 (.19)	1.60	2	.66

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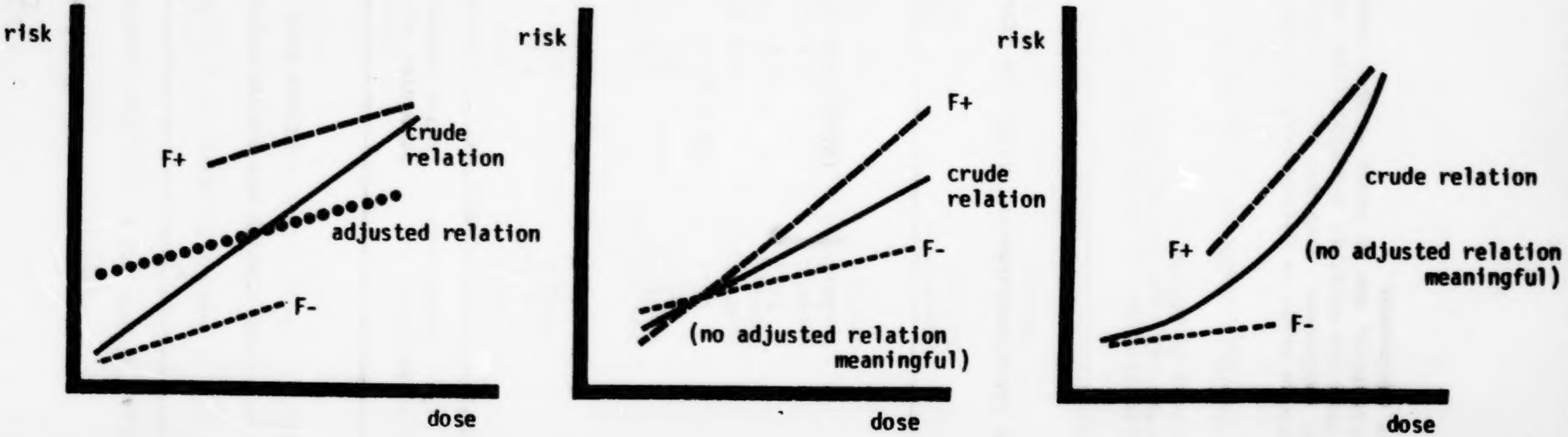
[1] See footnote 1 to table 7.4

[2] Excluding the lowest smoking-radiation group, for which the additive model predicted a negative risk.

FIGURE 7.1

ILLUSTRATION OF CONFOUNDING AND EFFECT MODIFICATION



(a) Factor F a confounder

(b) Factor F an effect modifier

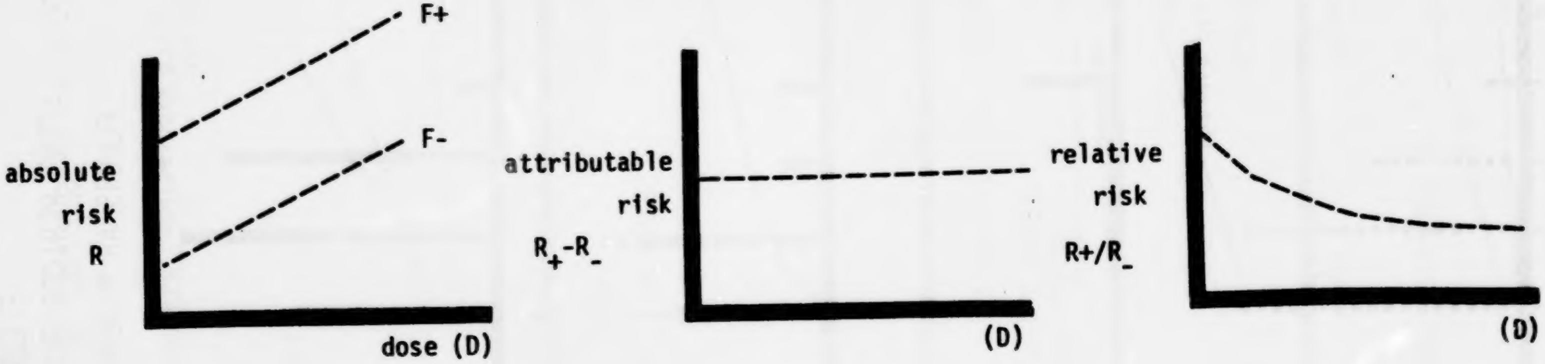
(c) Factor F both confounding and effect modifying

risk
F+
crude
relation
adjusted relation
F-
dose
risk
F+
crude
relation
F-
(no adjusted relation
meaningful)
dose
risk
crude relation
F+
(no adjusted relation
meaningful)
F-
dose

FIGURE 7.2

EFFECT OF CHOICE OF SCALE ON STATEMENTS OF EFFECT MODIFICATION BY SOME FACTOR F

(a) ADDITIVE MODEL



(b) MULTIPLICATIVE MODEL

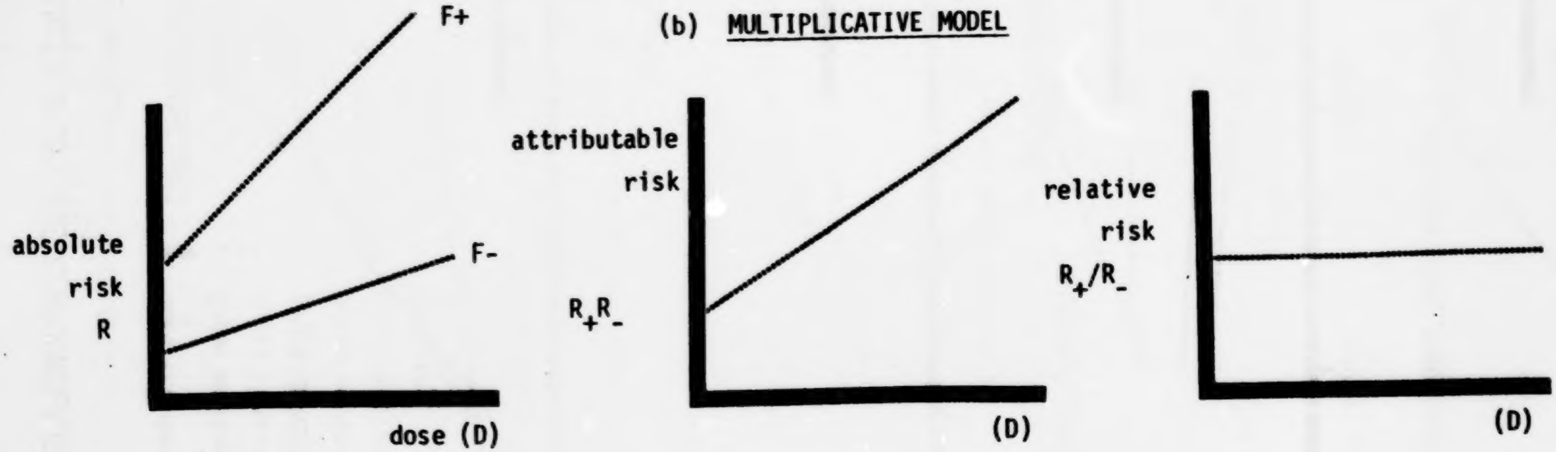


FIGURE 7.3

EPIDEMIOLOGIC LATENT PERIODS FOR LUNG CANCER AMONG THE NEWFOUNDLAND FLUORSPAR MINERS (SOURCE DEV80)

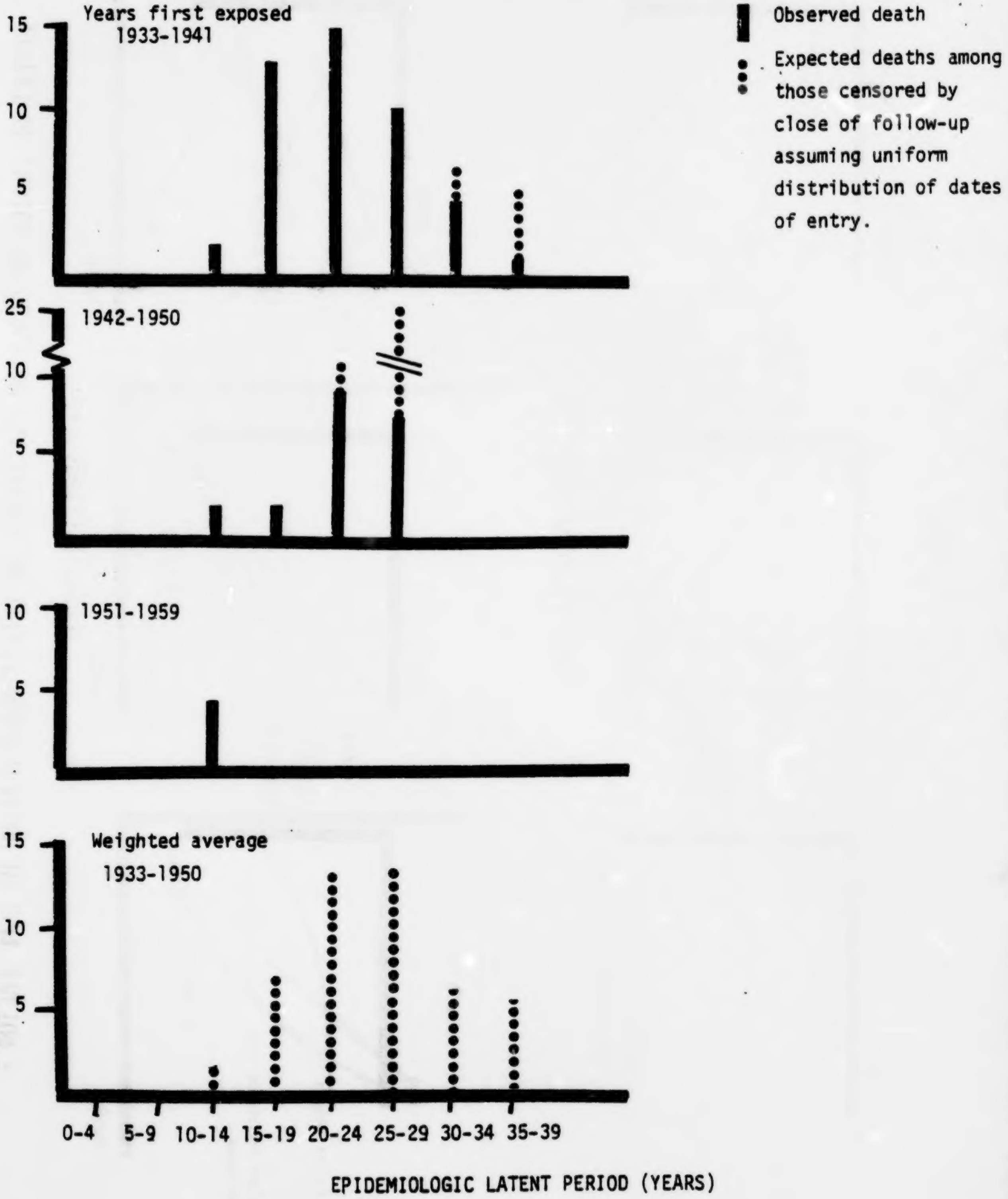


FIGURE 7.4

EFFECTS OF PROTRACTION OF EXPOSURE

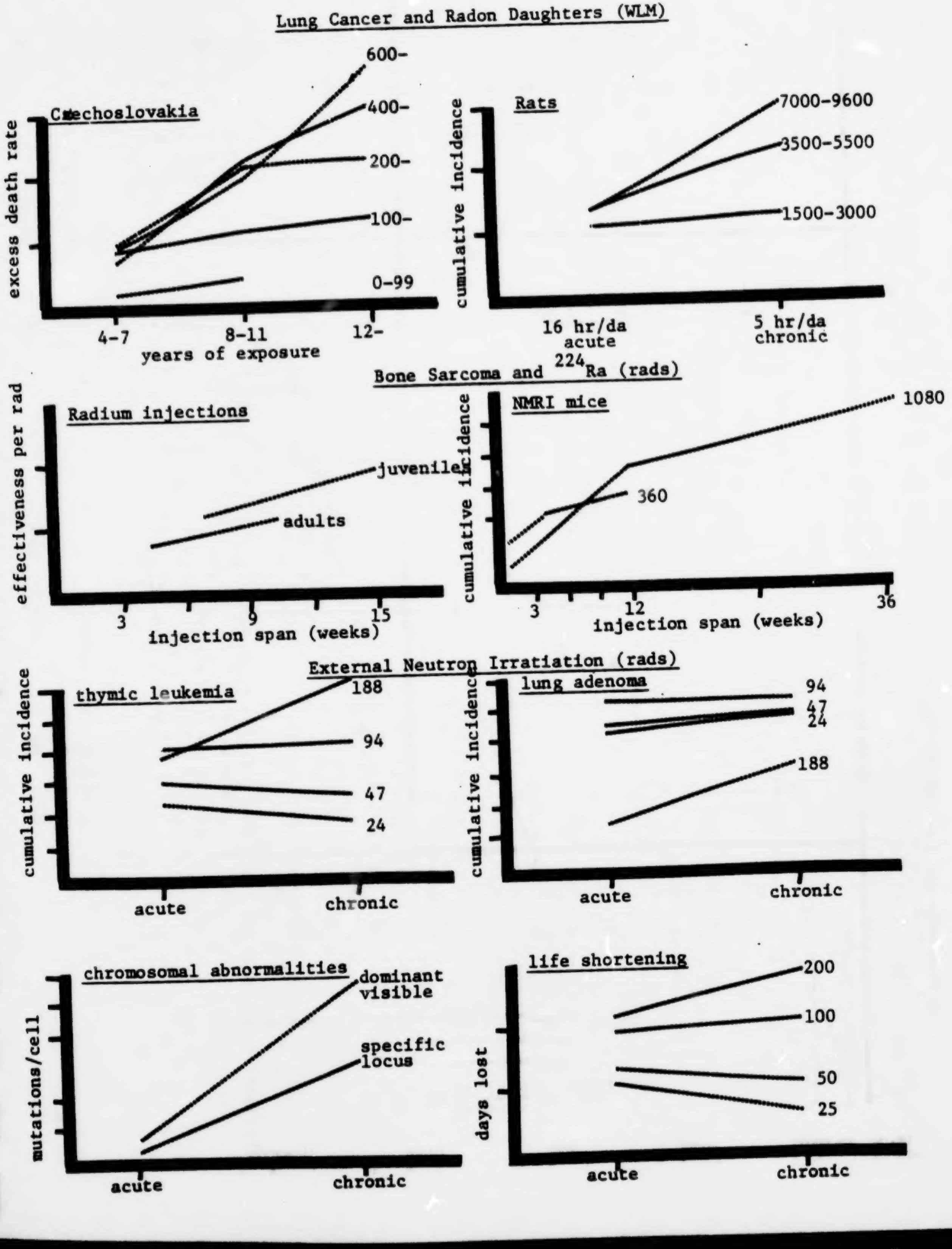
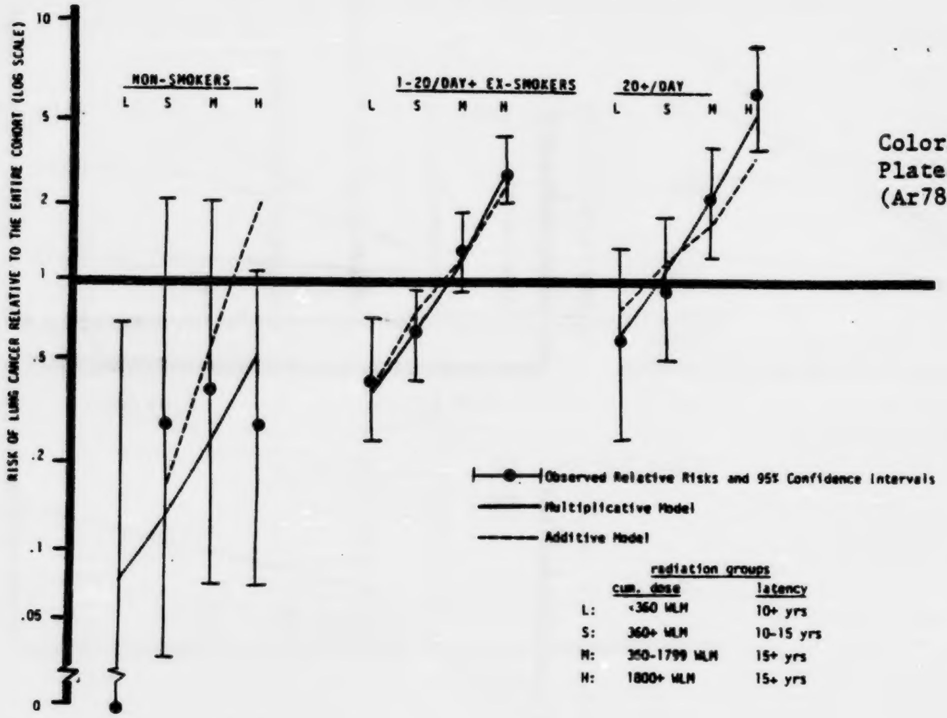
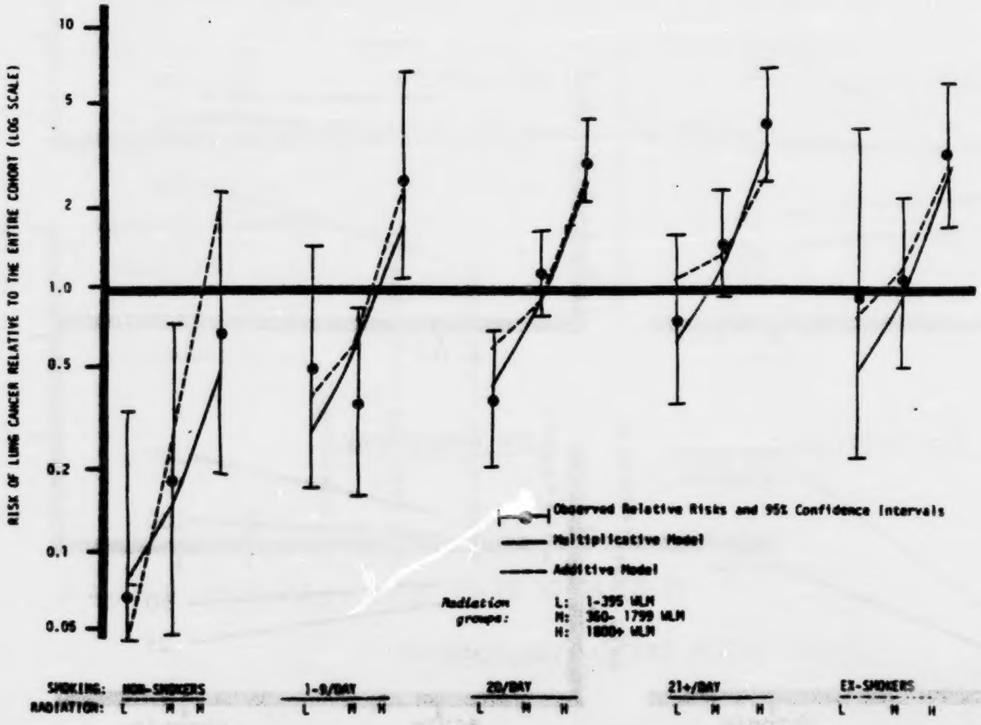


FIGURE 7.5

LUNG CANCER RISKS IN RELATION TO SMOKING AND RADON DAUGHTER EXPOSURE



Colorado
Plateau
(Ar78a)

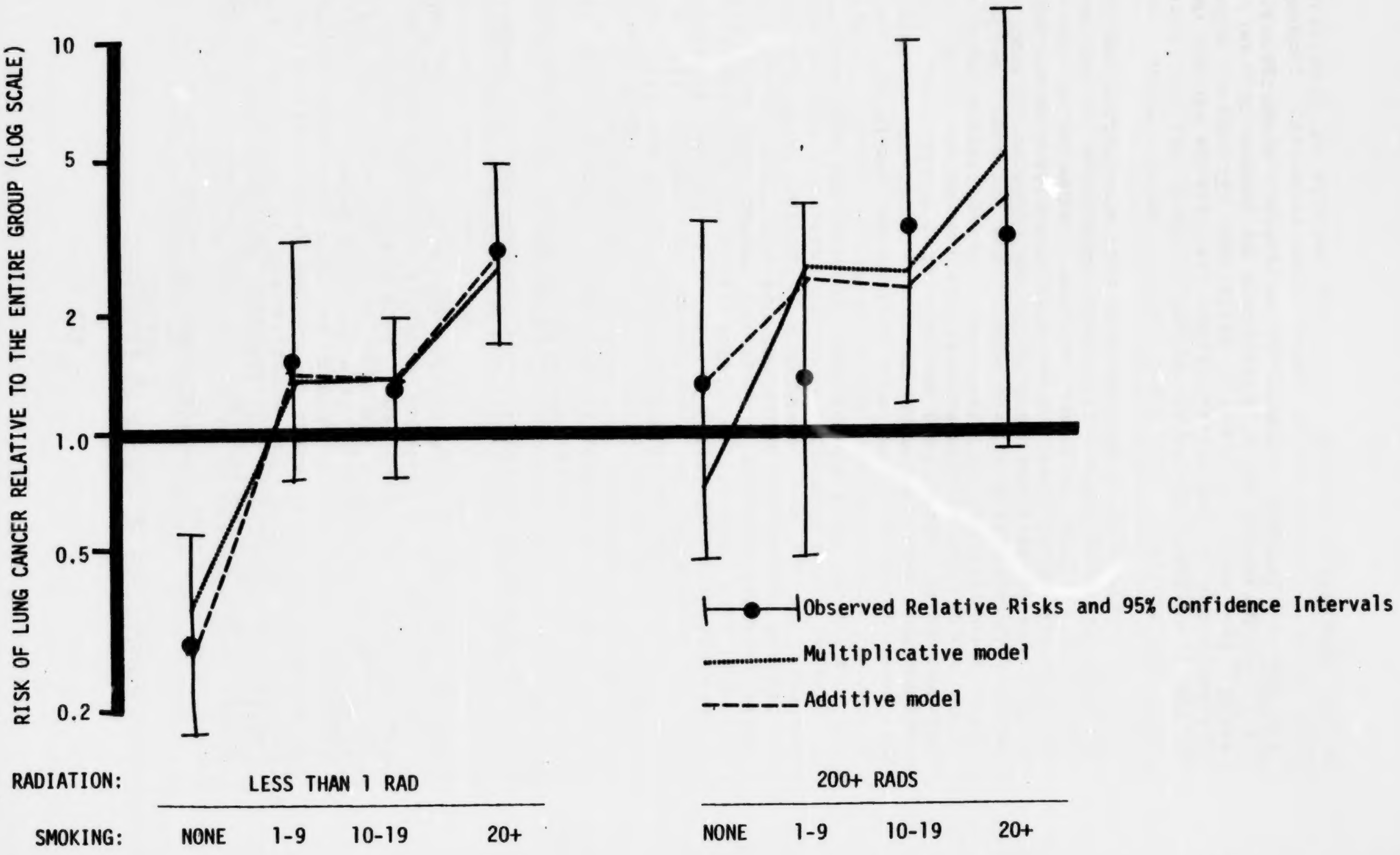


Colorado
Plateau
(Ar76)

FIGURE 7.6

LUNG CANCER RISKS IN RELATION TO SMOKING AND RADIATION EXPOSURE

ATOMIC BOMB SURVIVORS, 1950-1970 (Is 75)



CHAPTER 8

PRACTICAL IMPLICATIONS

This chapter is concerned with the implications of the evidence presented in the previous chapters for regulatory decisions. First, the limitations of the evidence (cf. Section 4.2.1.1 and 6.1) are discussed as they pertain to these decisions. While of course regulations can only be based on the best available evidence (even if inadequate), we wish to emphasize the need to consider the potential impact of possibly erroneous evidence, or evidence erroneously interpreted, the need to focus future research on areas where the evidence is weakest or most crucial, and the need to review decisions periodically in the light of new evidence.

8.1 LIMITATIONS OF THE EVIDENCE FOR REGULATORY DECISIONS

8.1.1 Limitations on shapes of relations

Inferences about overall shapes of relations are particularly sensitive to inappropriate choice of reference group for computing expected deaths and to failure to account adequately for latency (Section 4.2.1), but could also be affected by dose-related biases either in measurement of exposures or in ascertainment of deaths, or by effect modifiers which themselves were also associated with exposure. For example, of the six major studies of lung cancer (Section 5.1.1), the Ontario study is potentially the most affected by issues of latency because of its relatively short period of follow-up, and the Newfoundland study seems to have the least reliable reference group because of the much higher smoking rate in that cohort than in the rest of the province. Either problem might explain the concavity apparent only in these two studies. On the other hand, among the Colorado plateau miners, the highest exposure categories contain the largest contributions from other hard rock mining and the least reliable environmental assessments. Had these high exposures been overestimated (more than the low exposures), the exposure-effect relation would have been biased towards greater convexity (and conversely, had they been underestimated). As a final example, osteosarcomas were more likely to be ascertained among the radium patients, chemists, and dial painters with high doses than among those with low doses, thus possibly biasing relationships in the direction of concavity.

Inferences about shape have practical implications for extrapolation to low doses. The evidence in Chapters 5 and 6 imply that the use of a linear extrapolation may be approximately correct for high-LET radiation, but in view of these uncertainties, it cannot be guaranteed to be conservative (i.e. not to underestimate risks), as is commonly assumed for low-LET radiation.

8.1.2 Limitations on slopes of relations

Inferences about average slopes of exposure-effect relations are susceptible to biases similar to those enumerated above, but are probably most affected by errors in the assessment of exposure or disease. The effect of such errors depends on whether they are systematic or random and whether they are independent of exposure and/or disease.

Systematic errors will obviously bias any relationship. For example, if exposures tend to be uniformly overestimated by a common multiplicative factor at all doses, then the risk index will be underestimated by the inverse of that factor. On the other hand the addition of a constant amount of exposure would shift the curve to the right and the risk index would be underestimated by a factor which would vary with exposure. This latter scenario is likely if exposure levels were fairly constant and "wasted doses" not excluded from the exposure index (He79). Uniform underascertainment of disease (i.e. by a constant proportion in all exposure groups) will obviously reduce the absolute risk by the same proportion, but our real interest is in the excess risk per unit exposure, and this risk index will again be underestimated by a factor which would vary with exposure, unless the disease is extremely rare (Section 4.2.1).

Another type of systematic error is non-uniform, that is, associated with exposure or disease. Examples would be a greater overestimation of exposure or better ascertainment of disease at high than at low doses. Such non-uniform errors would change the shape of a relationship (Section 8.1.1) as well as its slope.

A certain amount of random error (neither uniform nor associated with either study factor) is inevitable in any measurement. For example, in any study with exposure estimates based on environmental measurements, there is bound to be considerable random error in calculating an individual's exposure. The effect of such errors is well known to bias estimates of relative risk towards unity (Co77b, Gl79, Br54, Fl73). For example, with a binary classification of exposure and disease, a 10% false positive and false negative rate in both factors is sufficient to reduce a typical excess relative risk to less than 30% of its true value (Th79a). Thus we must expect that the general tendency of epidemiologic studies would be to underestimate slopes, though the magnitude of the effect in environmental studies has not been established.

Inferences about slope have practical implications for setting standards. Thus, if some level of excess risk is deemed "acceptable", the estimate of slope can be used to predict the maximum level of exposure which would be permissible if risk were to be contained within that level. The choice of an "acceptable risk" is of course a social rather than scientific judgement, and is not considered further here; the methods of predicting risks are described in Section 8.2 and Appendix L.

8.1.3 Limitations on modifying factors

Inferences about modifying factors are limited primarily by the size of the smallest group being compared. As study of effect modification depends essentially on a three-dimensional cross-tabulation of the data, the average subgroup sample size will be smaller than for study of main effects. When the exposure, disease, and modifying factors are strongly correlated or non-uniformly distributed, some cells are bound to become even smaller. Thus in a cohort study of thousands of subjects, an inference on effect modification (say by smoking) could easily turn on a handful of non-smoking, lightly-exposed cancer cases, and thus have very little statistical precision. There is also potential for bias arising from any of the various measurement errors discussed above, but these errors would invalidate a conclusion about effect modification only if they were associated with all three factors in a complex way.

There are several practical implications of inferences on modifying factors. First, by describing how radiation-induced risks vary with age and time since exposure, they provide a basis for choosing between models for projecting risk estimates beyond the end of follow-up to an entire lifetime (Section 7.2.1.1 and 8.2). Second, they provide a basis for adjusting risk estimates derived from one population when generalizing to other populations having different distributions of the modifying factors. Finally, they allow separate risk estimates to be provided for specific subpopulations. However, the wisdom of having separate standards, say, for smokers and non-smokers, or for long- and short-service workers, raises social questions which are beyond the scope of this report.

8.2 IMPLICATIONS FOR ENVIRONMENTAL STANDARDS

8.2.1 Occupational standards for exposure to radon and thoron daughters

8.2.1.1 Basis of the current standard. The currently accepted maximum permissible exposure in mines in Canada to radon daughters is 4 WLM per year (this limit has implicit in it provision for gamma exposure as found in Ontario mines). This is primarily based on recommendations of ICRP59, and was brought into effect in Canada in 1975. In the United States the same figure applies. The historical development of this standard is outlined in Appendix D.

8.2.1.2 Risk estimates based on this standard. Under the 4 WLM/yr standard, the maximum exposure a worker could accumulate would be 200 WLM (i.e. continuous exposure to 1/3 WL for 50 years). Crude estimates of the resulting risks could be obtained by multiplying this factor by the attributable and excess relative risk indices given in Tables 5.1. For example, using the Czechoslovakia estimates, the attributable risk rate would be 200 WLM $\times 16.82/10^6$ PY-WLM = .00336/yr, which multiplied by an average life expectancy of 35 years (from age 40, the midpoint of the exposure interval) would lead to roughly an 11.8% additional lifetime probability of dying of lung cancer. Correspondingly, the excess relative risk would be 200 WLM $\times$ $1.92/10^2$ WLM = 3.84, which multiplied by an average lifetime risk of lung cancer in the general male population of 5.34% would lead to roughly a 20.5% additional lifetime risk of lung cancer.

Of course these crude calculations overlook a number of important issues: the 200 WLM level is not reached until age 65; some latent period must be assumed; and as lung cancer rates rise, the life expectancy is somewhat shortened. These various limitations can be overcome by using lifetable techniques as detailed in Appendix L. These techniques can be applied using a variety of assumptions about how radiation effects will accumulate in the future. Table 8.1 summarizes the risk estimates used in these calculations in relation to three basic types of assumptions:

1. Whether the attributable or relative risk indices described in Section 5.1 are used;

2. Whether these risk indices are a constant at all ages or vary with age; and

3. Over what period of time each exposure increment is assumed to be effective in increasing risk: (a) constant effectiveness over all subsequent times, (b) constant effectiveness beginning 10 years after the exposure increment, (c) constant effectiveness over an interval from 5 to 25 years after the exposure increment and no effectiveness outside this interval, or (d) varying in effectiveness according to a lognormal distribution with a 10-year median and a dispersion of 1.5. These assumptions about the biological latent period are depicted in Figure 8.1, together with the resulting cumulative effective exposure indices for exposures over an extended period of time.

The resulting estimates of excess lung cancers over an entire lifetime and average loss of life expectancy are provided in Table 8.2. These estimates span a considerable range, but not all are equally plausible. For example, for the reasons given in Section 7.2.1, we feel that the relative risk model provides a more appropriate basis for projection of lung cancer risks than does the attributable risk model; nevertheless, projections based on the attributable risk model are acceptable if the risk estimates are allowed to increase with age. Also, in view of the gradual decline in risks starting about 20 years after first exposure (Section 7.2.2), accumulation of exposures over the entire period at risk will probably lead to an overestimate of lifetime risk; there is also undoubtedly some latent period before each exposure increment begins to have an effect. The estimates based on a window of 5 to 25 years after each exposure increment probably represent lower bounds for the true lifetime risk, while those based on a 10-year minimum latent period occupy an intermediate position. However, all epidemiological studies have been reported in terms of exposure indices accumulated over the entire period and the resulting risk indices will therefore be valid only for that method of accumulating exposures in risk projections. When applied to the other methods of accumulating exposures, these risk indices will certainly be substantial underestimates, the amount of underestimation depending on the durations of exposure and follow-up in the various study populations. As discussed in Appendix L.2.1, we find that, considering a dozen plausible combinations of these two parameters, the risk index for the 10-year minimum latent period was underestimated on average by a factor of 1.65 and that for the 5 to 25 year window underestimated on average by a factor of 1.32. More reliable projections would therefore be obtained by multiplying the risk indices for the entire period by these factors. Finally, the projections using the lognormal distribution are based on the Colorado plateau data, which show much lower risks than the other studies, and therefore also require multiplication by the factors described in Section K.2.2 for comparability with the other risk estimates. Table 8.3 summarizes what we consider to be the most reliable risk estimates selected and adapted from Table 8.2; these estimates now average 13,379 excess deaths (1.99 years loss of life expectancy) and vary over a range of only about 3 or 4-fold, which we feel adequately describes the uncertainty involved in projection, in addition to the uncertainties inherent in the epidemiologic estimates of the risk indices on which they are based. The effect of these latter uncertainties can be described by scaling the lifetime risk estimates upward or downward proportionally for the various risk coefficients provided in Table 5.5. (This proportionality is only approximate, for as the lung cancer rates increase, the person-years to which they are applied decrease, so that lifetime lung cancers increase less than linearly.) Thus, for example, scaling our average projection of 13,379 excess deaths (based on the Czechoslovakia estimate of $2.01/10^2$ WLM) to the "best upper limit" of $2.28/10^2$ WLM would produce a "best" projection of 15,176 excess lung cancers (2.26 years loss of life expectancy) with a range from 3,594 deaths or 0.54 years of life (based on the Colorado study) to about 27,490 deaths or 4091 years of life (based on the Ontario study).

No directly comparable life-table calculations have been reported in the literature. The only two published reports we have seen which have used life-table methods (BEIR80 and Bu81) both express their findings in units of rads or rems instead of WLMs and for cancers of all or many sites combined rather than just lung cancer; we have therefore not attempted to reconcile their findings with ours. The lifetime risk indices recommended in

UN77 lead to a predicted risk of 4000 to 9000 excess lung cancers per 100,000 persons exposed to 4 WLM per year for 50 years, or 26% to 59% of our "best estimate" above; the reason for their lower estimate is their lower risk index and their assumption of a maximum of 40 years for the effect period (Section 5.1.3). Corresponding calculations based on the BEIR80 risk indices (Table 8.3) were similar to those we arrived at in other ways and are included in our "best estimate".

Considering the importance of smoking as a risk factor for lung cancer and the uncertainty about its interaction with radiation effects (Section 7.3), it is instructive to consider how these excess deaths would be distributed between smokers and non-smokers. It is now well established that the fact of smoking interacts multiplicatively with age effects, i.e. that a relative risk model applies (SG79), though such factors as age at starting and stopping smoking are important modifiers. However, there is some uncertainty about the forms of interaction of radiation with smoking and age. Limiting these to additive and multiplicative forms, four possible models can be considered, as described in Appendix L.2.3. Since the only directly observable data which could have provided estimates of the various risk indices (the Colorado study, Section 7.3) have not been reported in sufficient detail to allow all the indices to be calculated (and would in any event be substantially lower than the estimates just described), we have instead chosen to estimate these indices by partitioning the Czechoslovakian relative and attributable risk indices between smokers and nonsmokers in such a way that the total risk indices are the same. For this purpose, we have assumed that smoking confers a 14-fold relative risk (SG79) and that 40% of Canadian adult males are smokers (SG79). When these rates are then used in life table projections, the lifetime risks in the total population differ slightly from those given in Table 8.2 because the person-years are differently distributed between smokers and non-smokers, but the real interest is in how the deaths are distributed (Table 8.4). Thus if smoking and radiation interact additively, the additional deaths are distributed roughly in proportion to the size of the two groups, though in relative terms the increase is very much larger among non-smokers. If smoking and radiation interact multiplicatively, the relative increases are similar in the two groups, though in absolute terms, many more deaths occur among smokers.

It must be emphasized that these estimates are upper limits for an individual receiving the maximum permissible exposure under current regulations. In practice, virtually all workers would tend to receive lower exposures, both because few would work for a total of 50 years and because their exposures would vary in intensity, only occasionally reaching the peak of 4 WLM/yr. As noted in Appendix B, ICRP finds that in the non-mining nuclear industry, a limit of 5 rem/yr results in an average of about 0.5 rem/yr. If the same situation applied in uranium mining and if the average duration of employment were about 25 years, the average exposure would become only 10 WLM and the resulting excess risk 1/20 of the 15,176 deaths and 2.26 years of life lost quoted above, or 759 deaths (about 14% of the natural incidence) and 0.100 years of life lost. On the other hand, the evidence that protraction of dose increases risk (Section 7.2.3) suggests that our epidemiologic data (based on workers with considerably less than 50 years exposure) might underestimate risks to long service workers.

Finally, it is instructive to compare these risks to those in other industries. The industrial accident rate is frequently used for such comparisons (ICRP77, Bu81). Death rates for industrial accidents range from 60 per 10^6 PY for trades to 630 per 10^6 PY for mining and quarrying, with an average of 150 per 10^6 PY for all industry (Bu81). Adopting the figure of about 100 per 10^6 PY for "safe" industries and applying these rates to the age range 15-64 produces an estimated 436 lifetime excess deaths per 100,000 and an average loss of life expectancy of 0.16 years (Appendix L.2.2). Thus, the best estimate of 759 excess lung cancers resulting in the nuclear industry on average from the 4 WLM/yr standard amounts to 1.74 times the accidental deaths. On the other hand, industrial accidents occur at a younger age than lung cancers on average, so the average loss of life expectancy from radiation of 0.100 years amounts to only 63% of that due to industrial accidents.

Nevertheless, the wisdom of comparing lung cancer and accident rates in these ways is subject to question, and it would be more sensible to compare regulations for radon daughters to those for other carcinogens in the workplace. The best studied of these is asbestos, for which current occupational standards vary from 1 to 5 fibres/litre (f/ml). The Quebec asbestos mining data (McD80) suggest a relative risk index for lung cancer of 3.8 per 10^4(f/ml)·yr. Since asbestos is retained in the lung, accumulation of exposures over the entire period provides a sensible index of cumulative exposure. The resulting life table (Appendix L.2.2) for the 5 f/ml standard produces 456 excess deaths and 0.058 years loss of life expectancy, both less than 4% of the corresponding projections for the radon daughter standard. As there is no reason to believe the relation between average and maximum cumulative exposures would differ between the asbestos and uranium mining industries, this would suggest that even the highest asbestos standard is much more conservative than the radiation standard.

8.2.1.3 Mixed Radon-Thoron Atmospheres. The WLM/yr standard is based on the assumption that radon daughters are the cause of the lung dose. The presence of thoron daughters should influence this standard, as there will be additional dose to the lungs (and elsewhere); in exactly the same way, the WLM/yr figure should be reduced if significant gamma activity were present.

Appendix E shows that, under mine conditions, 1 WLM of radon daughters (here written WLM(Rn)) gives an effective dose equivalent of about 0.8 rem to the whole body, while thoron daughters give about 0.4 rem/WLM(Tn). This enables a calculation to be made of the total effective dose under various conditions of radon/thoron mixtures. From these, further calculations could give the degree to which the allowed WLM(Rn)/yr should be reduced in the presence of thoron daughters in order that the effective dose will not exceed the maximum permissible received by the body in the absence of thoron daughters. Such initial calculations for various levels of thoron daughters are summarised in Table 8.5. We note that Elliot Lake mines have been stated to have WL(Tn) values one half those of WL(Rn) (Co81); higher values are quite possible. For convenience, allowing 1 rem/yr from external radiation, the radon daughter exposure has been chosen to give 4 rem/yr (assuming 0.8 effective rem/WLM(Rn)).

8.2.2 Household exposure to radon daughters

8.2.2.1 Basis of the current criteria. "Clean-up" criteria have been established by the AECB for levels of radon daughters in houses at which action may be taken. These criteria were based on a survey of levels in a particular "control" community (rather than a judgement of what level would lead to an "acceptable" risk). The "primary criterion" is greater than 0.02 WL. This is not an average value throughout a house, but rather a level at which action should be taken if found anywhere in the house. This is usually the basement, and the average in the house is usually significantly lower. "Prompt Interim Action" is to be taken at greater than 0.15 WL while 0.01 WL serves as an investigation level. Further discussion is in Appendix G.

8.2.2.2 Risk estimates based on the primary criterion. The principles of risk projection for the 0.02 WL primary criterion for household radon daughters are essentially the same as described in Section 8.2.1.2, though there are a few minor differences. First, instead of assuming a 170 hour working month, we have based our exposure calculations on 17 hours per day at home, seven days a week. Second, we have assumed that "effective" dose rates at quiescent breathing rates are roughly 50% of those at active breathing rates (Section 7.5). Third, we have assumed exposure continues from birth to death and have made no adjustments for variation in lung volume or susceptibility with age (except as implicit in the relative risk model). Finally, the results are presented in Tables 8.2 to 8.4 in terms of lifetime excess risks of lung cancer for each 0.01 WL of actual exposure beyond normal background levels. Thus, the average of the adjusted projections is 1030 excess lung cancers per 100,000 and 0.146 years of life expectancy lost per 0.01 WL. This figure can also be scaled upward or downward as described earlier to provide an approximate range from 277 to 2116 deaths and 0.039 to 0.300 years.

The only comparable risk calculation is that of Evans et al. (Ev81) for continuous exposure to an estimated background concentration of 0.004 WL, leading to an attributable risk of 120 lung cancers per 100,000 persons. Scaling this figure to 17 hours per day at 0.01 WL produces an estimate of 212.5 per 10^5 persons, only 20% of our "best estimate". The difference is explainable by their preference for a risk index very much lower than those recommended either here or in the other major reviews (see Section 5.1.3).

The actual public health impact of the 0.02 WL criterion is difficult to evaluate for several reasons. First, exposure levels vary between locations in a house (generally being higher in basements than in usual living areas) and vary over time, so that a measured level on which action is based may over- or underestimate the family's actual average level of exposure. Second, except in special cases such as Port Hope, observed levels are "natural", although enhanced from what they would be in a completely ventilated area. Thus, in evaluating the effect of the standard comparison should be made against the lowest attainable (i.e. background) level at the site rather than against zero exposure. Estimates of this background level vary considerably (UN77), but a figure of 0.007 WL (one third of 0.02 WL) is not unreasonable as an average, with the expectation (see below) that many locations could have natural levels many times this. Third, even in regions where the standard requires intervention in some homes, it is to be expected that most homes would have levels on average substantially lower than this - in a survey of 13 Canadian cities, about 2.5% of homes were found to have in excess of 0.02 WL but the distribution of radon daughter concentrations was highly skewed, with geometric means ranging from 0.0009 to 0.0036 WL (McG80). Finally, the protraction effect may have led to even more underestimation here of the effect of life-long exposure than in the case of the occupationally exposed.

As shown in Appendix E, the equivalent doses to the bronchial and pulmonary parts of the lungs are both lower (in rems/Joule) for thoron daughters than for radon daughters. However, if the measured WLM is that for radon daughters (WLM(Rn)) and there is significant thoron present, the total biological effect may be greater than expected on the basis of the WLM(Rn) alone. In Elliot Lake mines, WL(Tn) values were found to be half those of WL(Rn) (Co81); this comes about because of the long half-life of the radon (compared to Tn) which means that most Rn is swept out of the mine. In houses, as in mines, the relative WL(Tn) to WL(Rn) will depend on the underlying rock and soil, the building structure, and the ventilation. Table 8.5 may be used to estimate total doses (and then to recommend maximum permissible levels of WL(Rn)) for various ratios of thoron and radon daughters. We note here that an equal mixture of daughters (WL(Rn) = WL(Tn)) will raise the effective dose equivalent to about 1.5 times the value expected if there were only radon daughters present. We also note (see Appendix E) that high thoron daughter levels may give significant doses to parts of the body other than the lung (this is taken into account in the calculation of effective dose).

8.2.3 Guidelines for radium in drinking water

8.2.3.1 Basis of the current guidelines. Canadian guidelines for radioactivity in drinking water are based on ICRP calculations, described in Appendix H. In 1978, Health and Welfare Canada (HWC78) adopted a "maximum acceptable concentration (MAC)" of 1% of the ICRP recommended annual occupational dose equivalent limit for continuous exposure and a "target concentration" of 0.1% of these ICRP limits. Table 8.6 gives the resulting ICRP and MAC figures for the isotopes of radium, the MAC figures being based on an average intake of two liters of water per day. A Toronto-based survey (Mo61) found levels of ^{226}Ra in well water averaging 1pCi/ℓ, and tap water averaging 0.3 pCi/ℓ, in other words, less than the target concentration of 2.6 pCi/ℓ.

8.2.3.2 Risk estimates based on these guidelines. Risk estimates (Table 8.6) for the short-lived ^{224}Ra are based on the study of German radium-injected patients (Ma78), and estimates for the long-lived ^{226}Ra and ^{228}Ra are based on the study of female radium dial painters (Ro78a), as described in Section 5.2.5. For the long-lived isotopes, we have not attempted separate risk calculations, because risk coefficients were not available separately and because the effect of the shorter half-life of ^{228}Ra should be approximately balanced by its higher MAC. The calculations for the short and the long lived isotopes are quite different, however, and are explained in detail in Appendix L.3.

For the short-lived ^{224}Ra, the risk index is provided in units of bone sarcomas per person-rad (average skeletal dose). Because the sarcomas tended to appear soon after injection, we have projected our risk estimates using a "current absolute risk" model, that is assuming that the additional age-specific sarcoma rate is proportional to the equilibrium body burden at that age. Thus, the calculation of cumulative lifetime risk can be done very simply without resort to life tables by multiplying the rate by the life expectancy (slightly modified because the estimated risk per unit dose is higher in children than in adults). Greater uncertainty is involved in calculating the equilibrium body burden at different ages, requiring assumptions (1) that intake is proportional to body mass, (2) that absorption from the gut to the blood varies from 80% in children to 20% in adults, (3) that deposition from the blood to the bone varies from 60% in children to 20% in adults, and (4) that the wet mass of the marrow-free skeleton is 10% of total mass at all ages. Because of uncertainty about these assumptions, the resulting risk projections must be considered [illegible] the largest contribution to life-time risk appears to result from childhood exposure because of the higher rates of retention, deposition and effectiveness which we have assumed.

For the long lived isotopes, the risk index is provided in units of bone sarcomas and head carcinomas per person-year-μCi (systemic intake). Because these tumors appeared over a very long time span, we have projected these risk estimates using a "cumulative absolute risk model", that is assuming the additional age-specific tumor rate is proportional to the cumulative systemic intake at a lag of five and ten years respectively. Again the estimation of systemic intake depends on assumptions about the rates of oral intake and absorption from the gut; we have taken the product of these two rates to be a constant at all ages, fixed at 20% of 700 Bq per year in adults or the equivalent in children (700 Bq is 1% of annual limit of intake as calculated by ICRP79). The life table calculations, described in Appendix L.3.2, can be approximated by multiplying the systemic intake rate, (700 Bq/yr) $(2.7 \times 10^{-5}$ μCi/Bq) (20%) = .00378 μCi/yr by the integrated person-years at risk, $(1/2)PY^2$, and by the risk indices, that is

$$\begin{aligned} \text{Cumulative risk} = {} & (.00378\mu\text{Ci/yr})\times \\ & [(2.36\text{sarcoma} / 10^5\mu\text{Ci-yr})(68\text{ yr})^2/2 \\ & + (1.98\text{ carcinoma} / 10^5\mu\text{Ci-yr})\ (63\text{ yr})^2/2] \\ & = 35.5\text{ tumors per }10^5\text{ persons.} \end{aligned}$$

In these calculations, we may have underestimated the systemic intake of children and the effectiveness of that exposure, but because the greatest contributions to total risk occur in adulthood, these assumptions are less critical than for ^{224}Ra. A more important assumption here would seem to be the choice of the cumulative absolute risk projection model. However, by far the most important assumptions are those affecting the estimation of systemic intake, both absorption from the gut and oral intake. We have assumed that the latter consists entirely of 2 liters per day of drinking water. However, radium, like calcium, might become concentrated in the food chain and thereby could lead to additional intake. Concentration factors of up to 100 have been reported (Ts63) in the bones of fish living downstream of a uranium mill, though the fish flesh had a concentration factor of 3 to 4. Taking the worst case (100×) and an intake of 20 g of fish per day, the radium intake via this route would be equal to that from 2 litres of drinking water of the same Ra concentration as that of the fish habitat. As most fish is eaten boned, the more likely intake via fish is an additional few percent on that from drinking water at the same concentration. In plants concentration can also take place; a factor of 20,000 exists being the highest and lowest concentrations of radium in foods (Tu58), with the highest concentration in Brazil nuts (a later measurement, Ah62, gave a concentration of over 100 pCi/g in these nuts). Cereals also have a higher activity than the average. As very few food plants are aquatic, no direct relationship exists between concentrations of radium in local water and concentrations in food plants. On average, in areas of normal background, intake of radium through food has been estimated to be about 1 pCi/day (UN77) or about 2% of the maximum acceptable intake from water under the Canadian standard. However, meat, milk, and vegetation may be more important pathways for certain other radionuclides, such as polonium, which are not bone-seekers. Human dose commitments for various radionuclides through various pathways have been extensively reviewed elsewhere (UN77, NRC79).

These risks seem to be very much smaller than those calculated for household exposures to radon daughters (Section 8.2.2.2). For the ICRP occupational limits, similar calculations based on a 50-year exposure to ^{226}Ra or ^{228}Ra would lead to about a 2.1% life-time probability of bone or head tumors. On the other hand, if the figure of 0.3 pCi/ℓ were representative of the average Canadian tap water concentrations, we would estimate that about 0.4 tumors per 100,000 persons would be attributable to background radium, in comparison with a natural cumulative risk of about 100 per 100,000 persons.

8.3 OTHER IMPLICATIONS

8.3.1 Credibility of low dose extrapolation

It has been frequently been argued that the natural background radiation level provides an upper limit to any estimate of the carcinogenic effect of low-levels of radiation, as the predicted effect could not logically exceed the natural incidence of cancer (see, for example, Co80). In an effort to refine this upper limit for lung cancer, it seems natural to use rates for non-smoking females before 1950, under the assumption that background radiation levels have not changed substantially over time. In this way, Cohen and Cohen show that the predicted lung cancer death rate, based on linear extrapolation of risk estimates down to an estimated 0.007 WL background level, exceeds this "natural incidence" and therefore conclude that the linear extrapolation is invalid.

This argument is subject to a number of epidemiological pitfalls, but one unstated assumption is crucial: the use of the absolute risk projection model. For reasons described in Chapter 7, we find that radiation effects may combine multiplicatively both with age and with smoking effects. If this were the case, then extrapolation of risk estimates to eras and subpopulations with lower natural incidences would see estimates of radiation effects reduced proportionally.

Thus, based on the estimates in Table 8.4, we calculate that at present rates, 721 lung cancer deaths per 100,000 males (or 13% of the observed number) could have been attributable to a background radon daughter level of 0.007 WL (acting alone as well as in combination with smoking). Under the multiplicative model, this same proportion, 13%, would be attributable to background radon daughters in pre-1950 non-smoking females, even though the absolute numbers would be considerably smaller. As this proportion is not unreasonable, we conclude that the natural incidence is not inconsistent with a linear low-dose extrapolation model.

8.3.2 Rotation of workers

Current regulations require that no worker be exposed to more than 5 rem of radiation in any year. This regulation is intended to maintain the risk for any individual to a reasonable minimum, but it is instructive to consider the public health implications of this policy. Let us suppose a certain total person-rems of exposure were needed to accomplish some task and consider the relative merits of distributing this exposure over a few or over many workers. If the true exposure-effect relation is linear, then the expected eventual toll of cancers produced is unaffected by how the exposures are distributed (except perhaps by second-order considerations such as latency or age). Spreading the total dose over many workers does of course protect each individual (though it makes it more difficult for those who develop cancer to mount a convincing compensation claim). If the true exposure-effect relation is non-linear, then the policy will have an effect on the expected eventual toll: if concave, the toll will be reduced; if convex, the toll will be increased. The magnitude of these effects depends on the degree of curvilinearity. For our best estimate of the exponent in the non-linear model, $\hat{c} = 0.916$ (Table 5.5), distributing 5000 WLM over 10 workers at 500 WLM each produces an "effective" exposure of $10 \times 500^{.916} = 2967$ person-WLM compared with 4368 effective person-WLM (or 47% greater) if the same total dose is distributed over 1000 workers at 5 WLM each. This is perhaps a rather extreme example as individual doses of 500 WLM would today be considered unacceptable and thus the 47% additional societal burden might be considered small in comparison with the desirability of protecting individuals.

8.3.3 Compensation

In principle, compensation is payable to workers (or their beneficiaries) who develop a recognized occupational disease, and who have a history of occupational exposure to some potentially causal agent, and for whom the link between exposure and disease is likely to have been causal rather than coincidental. Obviously an essential part of any compensation claim or litigation is concerned with appropriately documenting the histories of exposure and disease, and nothing more will be said of that here. A major source of contention, however, is the causality of the link; in the US, for example, 73% of contested occupational disease claims are fought over this issue (DOL79). Many factors are taken into consideration in such cases, including the age of the subject, the temporal pattern of exposure, the existence of other possible causal factors, clinical characteristics, and so on. However, the single most important piece of evidence is the amount of exposure, which must be shown to be "sufficient" to have produced the disease. Now if there is indeed no absolute threshold, then it follows that any dose, however small, might be sufficient to produce the disease and one could argue that therefore all workers with diseases of potentially occupational origin, ought to be compensated on a form of "no fault life insurance" basis without requiring proof of causality (Si81). However, the principle of "the balance of probabilities" has generally been used as a reasonable compromise: in other words, compensation is payable if the exposure is "likely" to have caused the disease, where "likely" has at least an intuitive if not explicit probabilistic meaning.

The evidence on exposure-effect relations in Chapter 5 has a direct bearing on this "balance of probabilities." It has been shown (Th79b, En80, DOJ78) that an individual with dose D and other confounding factors $\underline{C}$ the probability A that the exposure caused or in combination with $\underline{C}$ contributed to the development of his disease is $A = [RR(D,\underline{C}) - RR\ (0,\underline{C})]\ /\ RR\ (D,\underline{C})$. If we further accept the multiplicative model for exposure-confounder interactions (i.e. $RR\ (D,\underline{C}) = RR_1(D) \cdot RR_2(\underline{C})$ then the terms involving $\underline{C}$ cancel out and we are left with $A = 1- RR_1(0)\ /\ RR_1(D)$. Now if we assume that the exposure-effect relation is approximately linear with slope $\hat{\beta}$, then we finally arrive at

$$A = 1 - 1\ /\ (1 + \hat{\beta}D). \tag{8.1}$$

At the "doubling dose" $D_0 = 1/\hat{\beta}$, then $A = 1/2$ which in a strictly legalistic sense would be considered the "balance of probabilities" (ignoring all the modifying considerations emphasized above). Using our "best upper limit" of slope from Table 5.5, our estimate of this doubling dose is 1/.0228 = 44 WLM.

Thus provided compensation claimants were representative of all lung cancer cases arising in the populations on which our risk estimates are based, it follows that among those with a cumulative exposure of about 44 WLM, on average, 50% would have been radiogenic in origin, and this proportion would vary with exposure according to equation 8.1. Furthermore, under the relative risk model, age and smoking habit do not enter into this calculation. However, we certainly would not encourage the blind use of this 44 WLM as an arbitrary cutoff point for deciding whether or not a cancer was to be considered radiogenic in origin. The limitations of the epidemiologic evidence emphasized above, the uncertainty about any individual's exposure assessment, and above all, the need to take many other factors into account means that such judgements must remain an essentially clinical, subjective one.

TABLE 8.1

SUMMARY OF RISK COEFFICIENTS USED FOR LIFE TABLE PROJECTIONS

Interval over which exposures are accumulated	Method of Projection			
	Attributable As functions of age		Relative As functions of age	
	constant	varying	constant	varying
Entire period from first exposure to risk	$16.82/10^6$ PY-WLM from Czechoslovakia, Table 5.1	$10/10^6$ PY-WLM age 35-49 $20/10^6$ PY-WLM age 50-64 $50/10^6$ PY-WLM age 65+ from BEIR III p.390	2.01/10 WLM from Czechoslovakia Table 5.5	N.A.
Period from first exposure to 10 years before risk	same as above[1]	same as above[1]	same as above[1]	N.A.
Window from 5 to 25 years before risk	same as above[1]	same as above[1]	same as above[1]	N.A.
10-year median lognormal distribution of intervals before risk	$8.61 \times 10^{-5} \times D^{0.83}$ from US uranium miners where D is dose in WLME and A is age[2] (Table 7.2)	$2.26 \times 10^{-10} \times D^{0.83} \times A^{3.35}$	$0.13 \times D^{0.87}$ from US uranium miners where D is dose in WLME and A is age[3] (Table 7.2)	$6.36 \times 10^{4} \times D^{0.74} \times A^{-3.20}$

Notes

[1] These are underestimates of risk coefficient as the epidemiologic data was fitted to exposures accumulated over the entire period, not this window.

[2] For approximate comparability with the Czechoslovakia data, multiply by 6.78 (§K.2.2).

[3] For approximate comparability with the Czechoslovakia data, multiply by 4.84 (§K.2.2).

TABLE 8.2

PROJECTED EXCESS RISKS OF LUNG CANCER FROM EXPOSURE TO RADON DAUGHTERS

Interval over which exposures are accumulated	Method of projection: Risk coefficients as function of time:	Excess lung cancer deaths per 100,000				Average loss of life expectancy (years)			
		Attributable		Relative		Attributable		Relative	
		Constant	Varying	Constant	Varying	Constant	Varying	Constant	Varying
Household exposure to 0.01 WL beyond normal background levels for 17 hours/day from birth to death at quiescent breathing rates									
Entire period from first exposure to risk		738	989	1265	N.A.	0.187	0.142	0.159	N.A.
Period from first exposure to 10 years before risk		576	837	1080	N.A.	0.135	0.117	0.134	N.A.
Window from 5 to 25 years before risk		312	308	375	N.A.	0.096	0.050	0.051	N.A.
10-year median lognormal distribution of intervals before risk		112	175	150	154	0.035	0.028	0.020	0.028
Occupational exposure to 4 WLM per year from age 15 to age 64 at active breathing rates									
Entire period from first exposure to risk		9,655	13,434	16,734	N.A.	2.26	2.02	2.25	N.A.
Period from first exposure to 10 years before risk		7,095	11,686	14,942	N.A.	1.38	1.63	1.90	N.A.
Window from 5 to 25 years before risk		4,827	5,547	6,588	N.A.	1.27	0.99	0.99	N.A.
10-year median lognormal distribution of intervals before risk		1,093	1,630	1,636	1,318	0.32	0.31	0.26	0.25

N.A. No risk coefficient available

TABLE 8.3

SUMMARY OF ADJUSTED ESTIMATES OF LIFETIME LUNG CANCER RISKS FROM EXPOSURE TO RADON DAUGHTERS

Risk model	Exposure accumulation interval	Adjustment factor	Excess cancers per 100,000 population	Average loss of life expectancy (years)
Additional 0.01 WL above normal background 17 hours/day from birth to death at quiescent breathing rates				
Attributable[1]	entire period at risk	1.00	989	0.142
Attributable[1]	up to 10 years before risk	1.65	1,380	0.194
Attributable[1]	5-25 years before risk	1.32	407	0.066
Attributable[1]	10-year lognormal distribution	6.74	1,176	0.186
Relative	entire period at risk	1.00	1,265	0.160
Relative	up to 10 years before risk	1.65	1,782	0.221
Relative	5-25 years before risk	1.32	495	0.067
Relative[1]	10-year lognormal distribution	4.84	747	0.134
Average of above estimates			1,030	0.146
Additional 4 WLM/year above normal background from age 15 to 64 at active breathing rates				
Attributable[1]	entire period at risk	1.00	13,434	2.025
Attributable[1]	up to 10 years before risk	1.65	19,282	2.682
Attributable[1]	5-25 years before risk	1.32	7,322	1.306
Attributable[1]	10-year lognormal distribution	6.74	10,988	2.079
Relative	entire period at risk	1.00	16,734	2.247
Relative	up to 10 years before risk	1.65	24,655	3.130
Relative	5-25 years before risk	1.32	8,236	1.236
Relative[1]	10-year lognormal distribution	4.84	6,380	1.232
Average of above estimates			13,379	1.992

[1] Based on risk estimates varying with age provided in Tables 8.1 and 8.2.

PROJECTED EXCESS RISKS OF LUNG CANCER FROM EXPOSURE TO RADON DAUGHTERS IN RELATION TO SMOKING STATUS

(assuming smoking interacts multiplicatively with age effects)

Interaction of radiation with		Excess lung cancer deaths per			Average loss of life expectancy (years)		
Age	Smoking	60,000 Non-smokers	40,000 Smokers	100,000 Total	Nonsmokers	Smokers	Total
Household exposure to 0.01 WL beyond normal background levels for 17 hours/day from birth to death at quiescent breathing rates							
Additive	Additive	469	271	740	0.19	0.18	0.19
Additive	Multiplicative	76	609	685	0.03	0.41	0.18
Multiplicative	Additive	813	457	1,270	0.17	0.15	0.16
Multiplicative	Multiplicative	132	1,020	1,152	0.03	0.33	0.15
Occupational exposure to 4 WLM/yr from age 15 to 64 at active breathing rates							
Additive	Additive	6,137	3,547	9,684	2.32	2.17	2.26
Additive	Multiplicative	1,044	7,428	8,472	0.39	4.46	2.10
Multiplicative	Additive	10,726	6,069	16,795	2.35	2.10	2.25
Multiplicative	Multiplicative	1,958	11,596	13,554	0.41	4.22	1.94

TABLE 8.5

DOSE ADDITIONAL TO THAT FROM 5 WLM(Rn)/yr BECAUSE OF PRESENCE OF THORON DAUGHTERS

Radon daughter exposures		Additional thoron daughter exposures		Total effective rems/yr
WLM(Rn)/yr	Effective rems/yr	WLM(Th)/yr	Effective rems/yr	
5.0	4.0	0.00	0.0	4.0
5.0	4.0	1.00	0.4	4.4
5.0	4.0	2.50	1.0	5.0
5.0	4.0	3.75	1.5	5.5
5.0	4.0	5.00	2.0	6.0
5.0	4.0	7.50	3.0	7.0
5.0	4.0	10.00	4.0	8.0
5.0	4.0	20.00	6.0	12.0

TABLE 8.6

LIFE TABLE PROJECTIONS OF BONE SARCOMA AND HEAD CARCINOMA RISKS

BASED ON THE ABSOLUTE RISK MODEL

Isotope	Half Life	Maximum Permissible Occupational Limit (ICRP79) (Bq/yr)	Canadian Maximum Acceptable Concentration in Drinking Water (pCi/ℓ)[1]	Risk Coefficient	Projected lifetime risk of radium-induced cancers per 100,000 persons at the Canadian standard
^{224}Ra	3.62 days	300,000	111	10-20/10^{5} rads[2]	15
^{226}Ra	1600 years	70,000	26	4.3/10^{5} PY - μCi[3]	38
^{228}Ra	5.75 years	90,000	33		

[1] (1% of ICRP ALI in Bq/yr) (27pCi/Bq) / (2ℓ /day water consumption) (365 days/year)

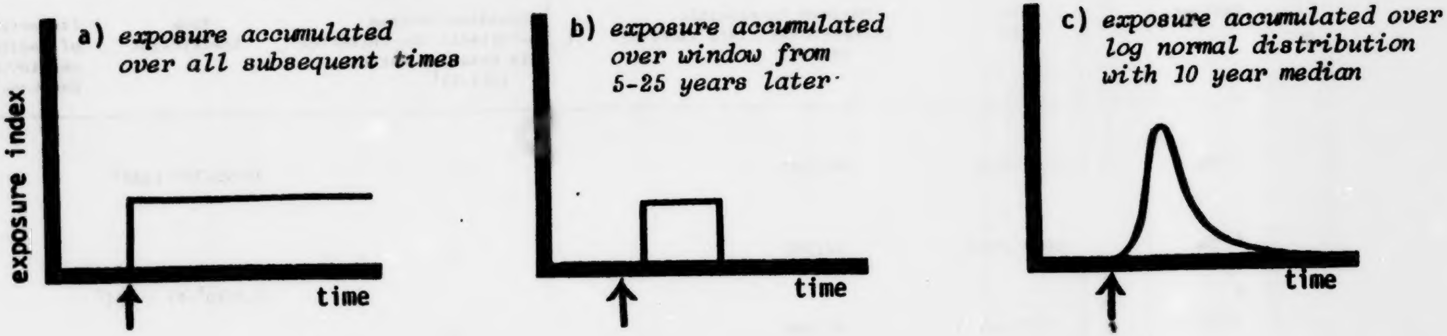
[2] Risk of bone sarcoma only, estimated from study of German radium injected patients (Ma78). See Table A4.4 for life table calculatons

[3] Combined risks of bone sarcoma and head carcinomas, estimated from study of radium dial painters (Ro78a). See Table A4.5 for life table calculations

FIGURE 8.1

INDICES OF CUMULATIVE EXPOSURE USED FOR LIFE TABLE PROJECTIONS

Effects resulting from instantaneous exposure

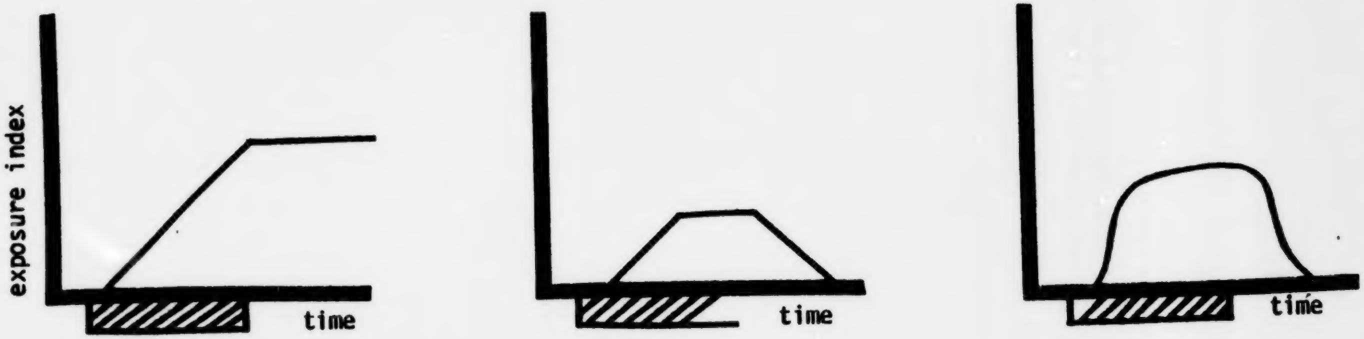

a) *exposure accumulated over all subsequent times*

b) *exposure accumulated over window from 5-25 years later*

c) *exposure accumulated over log normal distribution with 10 year median*

exposure index
time
time
time

Effects resulting from exposure over an extended time interval


exposure index
time
time
time

CHAPTER 9

CONCLUSIONS AND RECOMMENDATIONS

9.1 CONCLUSIONS REGARDING FINDINGS

9.1.1 Lung Cancer

1. The lung is a major radiosensitive site and for short-lived or insoluble inhaled alpha emitters, it is the primary concern.

2. Risk estimates under linearity range from 2.0 to 30.4 per 10^6 PY-WLM on an absolute risk basis or from 0.31 to 3.97 per 10^2 WLM on an excess relative risk basis (Table 5.1). Our best estimate for the excess relative risk is 2.28 ± 0.35 per 10^2 WLM, which gives a doubling dose of 44 WLM.

3. Considering the differences in populations and methods, and comparing these results with those of other epidemiological studies (such as on asbestos) there is a remarkable degree of agreement between the various studies; only the Colorado plateau data stand out as giving very much lower risk estimates than the other studies of miners.

4. Comparisons between studies indicate a striking inverse relationship between mean exposure and mean excess risk per unit dose (Figure 5.1) which appears to suggest non-linearity. However, such comparisons are very susceptible to confounding by differences in study populations, methodology, etc. Therefore, we feel only comparisons within studies can hope to offer unconfounded evidence on the shapes of dose-effect relations. Five mining populations offer the possibility of making such internal comparisons (Figure 5.2 and Tables 5.2 and 5.3). However, since none alone is sufficiently large and sufficiently without methodological problems to resolve the issue of the shape of the dose-response relationship convincingly, we have chosen to combine the studies in various ways, while allowing a separate estimate of slope in each (Tables 5.4 and 5.5). Thus on the first line of Table 5.4 we have constrained all studies to a common relationship of the general form $RR = (1 + b_i D^c) 0.5^{D/d_{1/2}}$ and have found the best fit of all the data with a common value of c and d but allowed a separate value of b (slope) for each study. In this way we hope to obtain the greatest possible power for detecting nonlinearity while avoiding confounding.

5. There is some suggestion of convex behaviour, i.e. $c < 1$. However, the data available does not provide a reliable basis for this conclusion, primarily because of inadequate treatment of latency and unreliable reference groups for computing the number of expected deaths in the studies published. Taking them at face value, four of the six studies indicate mild convexity and two studies indicate the reverse (Table 5.3); these last two are methodologically the least reliable. The data are inadequate to

distinguish between low-dose nonlinearity (best exponent $\hat{c}$ = 0.92) and linear with cell killing (best "half dose" for cell killing, $\hat{d}_{1/2}$ = 8774WLM), though the latter fits marginally better (P values 0.38 and 0.49 respectively, Table 5.4).

6. Although the fit to all studies combined (with separate slopes) can be significantly improved by the addition of a cell killing term (with or without an exponent suggesting convexity at low doses), they are also consistent with a simple linear relation ($p = 0.32$). Nevertheless, there is no justification for assuming that linearity would be a conservative basis for radiological protection for high-LET effects (as is widely held to be true for low-LET).

7. On the basis of a linear dose-response model with a constant relative risk of 2.28 per 10^2 WLM, the 4 WLM/yr standard for occupational groups could increase the lung cancer risk of an individual working all his life at the maximum by a factor of from 2.4 to 6.2 (best estimate 3.8) depending on how exposures are accumulated and risks projected (Table 8.3).

8. This is of course an estimate of the maximum risk obtained at 50 years of constant exposure to the maximum level of 4 WLM/year. It should be recognized that average exposures and hence average risks would be very much lower. ICRP77 notes that in the non-mining nuclear industry a maximum permissible dose of 5 rem per year results in an average value about ten times lower, and it is with that expectation that the 5 rem/year limit applies. If this situation applied as well to uranium mining, we estimate that the 4 WLM/yr standard would on average over the entire industry produce a 10 to 20% increase in the risk of lung cancer. While this is still a significant public health concern, the lung cancer risk would be small in comparison to the other hazards of mining (e.g. accidents and respiratory disease).

9. In Ontario mines and perhaps others, thoron also contributes to the dose but is not taken into account in the measurements of WLM, which only consider radon daughters. The total (weighted) effective dose due to thoron daughters may be taken as 0.4 rem/WLM(Tn), to be compared with 0.8 rem/WLM(Rn). Corresponding to a 4 WLM(Rn) limit in a pure radon (plus daughters) atmosphere would be an 8 WLM(Tn) limit in a pure thoron (plus daughters) atmosphere; in a mixed atmosphere, the 4 WLM(Rn) limit would have to be appropriately reduced (Table 8.5).

10. On a similar basis, a 0.02 WL maximum for homes could increase the lifetime lung cancer risk by about 40% above the level for a hypothetical zero exposure (Table 8.3). However, this is the predicted increase for a lifetime of additional 0.02 WL exposure beyond normal background levels. Estimates of these vary widely but might reasonably be as much as one third of 0.02 WL. Furthermore, the radon levels vary considerably over time and between locations within a home but might generally be lower

in usual living areas than in the basements (where the maxima are commonly measured). Finally, no adjustment has been made for differences in attached fractions between homes and mines or any other differences between mining and general populations, such as sex or smoking habits.

11. At an estimated mean lifetime exposure of about 10 WLM of background radon daughters, we calculate that about 10 to 20% of lung cancers are attributable to this cause. This attributable risk, based on today's rates in men, is larger than the total lung cancer risk in the pre-smoking era, and therefore looks unreasonable. However, if smoking interacts multiplicatively with other carcinogens (as suggested for smoking in conclusion 13 below) then populations or eras with lower rates will have proportionately lower radiation effects; another possibility is that the relative risks obtained from miner data are not applicable (perhaps because of unknown synergistic factors in the mines) to other populations.

12. Absolute risks increase with age whereas relative risks are either constant or decrease with age (Tables 7.1 and 7.2). This, together with the greater consistency of relative than absolute risk estimates from study to study, indicates that the relative risk model is a more appropriate basis for projecting lifetime lung cancer risks.

13. The interaction with smoking appears to be intermediate between additive and multiplicative models (Tables 7.6 and 7.7). Present data is inadequate to exclude either possibility, but on balance the multiplicative model is favoured.

14. The latent period distribution has a median of about 15 to 25 years if measured from first exposure (Table 7.5 and Figure 7.3) or about 10 to 15 years if measured from each increment of exposure (Table 7.4 and Lu71). Some tapering off in risk is apparent following the median, but risks continue to be substantially elevated beyond natural rates up to 30 or 40 years after exposure, the maximum time for which follow-up data is presently available.

15. The most common cell type associated with alpha radiation induced cancer is small cell anaplastic (type 2), but all types (particularly 1 and 3) can be affected. Until better dose-response data for each type become available, we feel that cell type should be given little weight in compensation considerations.

16. Protraction of dose appears to increase risks of lung cancer (and other effects) for high-LET radiation (Figure 7.4). For this reason, epidemiologic studies of populations exposed for relatively short periods may underestimate the risks of life-long exposure.

9.1.2 Bone sarcoma and head carcinoma

17. Exposure to radium and other bone-seeking radionuclides (e.g. plutonium, thorium, neptunium) can cause bone sarcomas. Some of these isotopes (apparently those which include radon as daughters, e.g. ^{226}Ra) can also induce carcinoma of the mastoid air cells and paranasal sinuses ("head carcinomas").

18. Bone sarcomas in the radium dial painters (^{226}Ra and ^{228}Ra) appear to show a concave dose-response relation at low doses (Figure 5.3) but this could be an artefact of incomplete ascertainment; head carcinomas in this group show a linear relation (Figure 5.4). ^{224}Ra-injected patients also show a linear relation (Figure 5.3). Animal experiments show a variety of patterns including convex and concave depending on the isotopes and animals used (Figure 5.1).

19. Our risk estimates in human studies assuming linearity are 2.4 per 10^5 PY-μCi (bone sarcoma) and 2.0 per 10^5 PY-μCi (head carcinoma) for systemic intake of ^{226}Ra and ^{228}Ra, and 20 per 10^5 person-rad (children) to 10 per 10^5 person-rad (adults) for average skeletal dose due to ^{224}Ra (Table 5.7). In view of the possible underascertainment and uncertainty about the true shape of the dose-response curve, these estimates are not necessarily conservative.

20. Based on these estimates, we calculate that lifetime ingestion of 2 liters per day of water at the current Canadian maximum acceptable concentration (26 pCi/ℓ for ^{226}Ra, see Appendix H) could lead to a life-time risk of 15 to 40 radium-induced cancers per 100,000 person (Table 8.6). However, we emphasize that these calculations are even less reliable than those for radon daughters (conclusions 7 and 10 above). In particular, we have not taken any account of additional intake possibly resulting from any aggregation of radium from water through the food chain, though for radium this does not appear to be an important pathway.

20. Children appear to be at higher risk than adults, both because their average skeletal dose per unit intake is larger and because that dose appears to have greater effectiveness (Table 7.3).

22. Both humans and mice exposed to ^{224}Ra show an increase in risk per unit dose with increasing duration of exposure (Figure 7.4). This phenomenon has not been studied for long-lived radioisotopes.

23. No major health effects of plutonium or of any other radionuclide except thorium (in thorotrast) have yet been demonstrated in human populations. However, none of the studies that have so far been published are of sufficient size to have any statistical power for detecting such effects, unless the risks had been very much larger than anticipated (Appendix I.2).

9.1.3 Other effects

24. A number of other somatic effects, both neoplastic and non-neoplastic, have been suggested to be related to exposure to alpha emitters (Table 5.8). However, most of these still require independent confirmation and the risk estimates provided should be considered as highly tentative.

25. Data on genetic effects of alpha radiation are very limited and restricted to animals (Section 6.2.4). These indicate that the maximum permissible amount of plutonium (for example) would lead to a dose to the testes of only about 0.3% of the generally accepted doubling dose for the mutation rate, while continuing intake of Pu from water which met the Canadian "maximum acceptable concentration" guideline could result in a dose 100 times smaller than this.

9.2 RECOMMENDATIONS FOR FURTHER STUDY AND ACTION

9.2.1 Problems associated with radon daughters

1. In view of the likelihood that inferences about shapes of exposure-response relations may be confounded by latency, measurement errors, protraction, smoking, and choice of reference groups, these conclusions should be considered to be highly tentative. However, as the necessary data already exist for several mining populations, many of these limitations could be overcome relatively quickly by reanalyses such as those suggested in Appendix M. We therefore recommend that linearity be treated only as a temporary ad hoc basis for interim standards, which should incorporate a "safety factor" to allow for the possibility of convexity; this safety factor need not be more than two-fold (Table 5.6). These conclusions should be reviewed after better analyses have been carried out on existing or improved data.

2. The Ontario and Newfoundland mining populations (and possibly others) should continue to receive the best possible follow-up. In particular, efforts should be made to obtain smoking histories (perhaps only on lung cancer cases and a sample of appropriately matched controls (Li77)), to evaluate the contribution of radiation to the reported risks of gastrointestinal and skin cancer, and to use the best available statistical methods.

3. Prospective studies of sputum cytology are needed to determine the predictive value of these signs and to establish whether their longitudinal changes are dose-related, in order to evaluate its usefulness as a screening tool. Cross-sectional studies at Eldorado Nuclear Ltd. (Uranium City, Sask., see appendix I.2.9) should be expanded with long-term [illegible] observations, and the feasibility of initiating new studies in Ontario uranium miners should be considered.

4. The clinical significance of chromosomal abnormalities in lymphocytes, their dose-relatedness, and their association with lung cancer should be studied in order to evaluate their usefulness for monitoring the possible health effects of low-

level radiation. Such studies could also be initiated in these same populations.

5. Consideration should be given to initiating a cohort study of family members of Ontario uranium miners during the 1950-60 boom and a case-control study of lung cancer in relation to radon daughter levels in homes. Of the two, the case-control study would probably be the more feasible starting point. Using the relative risk index of 2.28 per 10^2 WLM and accumulating exposures in the same way as described in Section 8.2, we estimate that if the standard deviation of household radon daughter levels were 0.005 WL, then a sample size of about 500 cases and 500 controls would be sufficient to demonstrate a significant association with lung cancer risk at the $\alpha = 5\%$ significance level and $1-\beta = 90\%$ power. The statistical power of the design could be further increased (or the sample size reduced) by sampling cases and controls from populations with the largest possible variability in exposure, for example by including substantial numbers from areas shown on previous surveys to have relatively high levels. Should it prove feasible to identify and trace family members of Ontario uranium miners, similar sample size calculations could be easily done.

6. Much better information must be obtained on dose received by individuals. Individual radon and radon daughter detectors should be developed and used. In a few locations, measurement of radon and thorium daughters (1.76 and 2.6 MeV gamma rays) should be made immediately after leaving the mine to make valid estimates of retained fractions to compare with "working levels".

7. The criteria for awarding compensation for lung cancer in radiation workers should be reexamined in the light of the evidence contained herein. We suggest that on average, 50% of lung cancers with an accumulated exposure (at some point before death) of about 44 WLM (the "doubling dose") would have been radiogenic in origin, and under the multiplicative-relative risk model, this fraction is not substantially altered by age or smoking history. However, this figure should be considered only as an overall guideline for a large population; for any individual, the temporal pattern, clinical history and other factors would have to be considered. Nevertheless, some more objective and equitable basis for such decisions would be desirable and the onus of establishing causation should not be placed on the individual claimant.

8. Important improvements may be possible in mine design and ore handling. This would involve, for instance, the full input during the design process of radiological data on ore and of its health physics implications. On these bases, appropriate ventilation strategy could be planned. From the point of ore handling, broken ore (with a large surface to volume ratio) should be removed quickly and stored above ground with a suitable dirt cover (the emanating coefficient of crushed ore is 3 or 4

times that of "core sized" ore). Haulage ways for such broken ore should be kept separate from air ways.

9. In our view, the present 4 WLM/yr maximum does not provide sufficient protection to an individual who works at that level for an entire lifetime, though for an entire group of uranium workers the average risk resulting from the use of this individual maximum might be considered acceptable. Since the intention of the standard should be to control this average risk, as well as the maximum risk to individuals, we recommend that regulations setting permissible annual exposures be supplemented by additional explicit requirements that average exposures to all relevant (i.e. potentially exposed) workers in a company be very much lower.

It is also desirable that few workers ever accumulate total lifetime exposures approaching the maximum possible under present regulations (approximately 200 WLM). However, we see no easy way to give this goal force. Compulsory rotation of workers before they reach excessive doses would provide a measure of individual protection, but would not appreciably alter the public health problem, and could lead to claims of job discrimination if the low-dose jobs were less remunerative or less attractive in other ways. We therefore recommend that lower maximum individual doses be encouraged by education of the workers themselves, maintenance of low average doses, and non-discriminatory policies of job rotation.

9.2.2 Problems associated with long-lived alpha emitters

10. Again, the risk estimates quoted above should be considered as highly tentative until better analyses of existing data have been carried out. These analyses (particularly the radium dial painters) should focus on deriving an appropriate exposure-time-response model for life table projection, taking into account age, latency, and protraction effects. A comparison of the effects of the long- versus short-lived isotopes might be particularly instructive.

11. The incompleteness of ascertainment will continue to be a major limitation of these data. Nevertheless, they will probably remain the best available basis for setting standards for bone-seeking radionuclides, so the on-going efforts to define and trace an epidemiologically suitable cohort of radium-exposed persons should be strongly encouraged.

12. Better data is needed on the relation between water standards for radionuclides and actual systemic levels, particularly as a function of age. This might be obtainable by review of ecological studies of the accumulation of radionuclides in the food chain and of metabolic studies of their ingestion from all sources and subsequent absorption and retention. Such a review would be beyond the scope of this report.

13. In view of these uncertainties, consideration should be given to initiating epidemiologic studies of body burdens and cancer incidence or mortality comparing communities with very different levels of radioactivity in drinking water.

14. Consideration should also be given to the feasibility of identifying and tracing other populations potentially exposed to plutonium or other radionuclides. For example, those involved in the clean-up of the 1958 accident of the Chalk River NRU experimental reactor were potentially exposed to plutonium and other mixed fission products (Hu60) in addition to gamma radiation. Such populations should be given the best feasible epidemiologic study as a means of testing the effectiveness of radiological protection measures as they were actually employed in past clean-up operations.

9.2.3 Utility of animal studies

15. Animal studies have a number of limitations affecting their relevance to humans, notably differences in the nature of the tumors, degree of inbreeding, shorter lifespan in relation to latent periods, and protection from other carcinogens (Section 6.1.3). Nevertheless, they could provide insight into a number of aspects which are difficult or impossible to study in humans.

16. Experimental studies of lung cancer in relation to high-LET radiation and particularly radon daughters are presently quite inadequate. Larger studies at lower doses with a variety of animal models could usefully contribute to our understanding of the shape of dose-response relations.

17. Experimental studies could also contribute to our understanding of synergistic effects with other carcinogens, particularly radon daughters and tobacco smoke. However, to be relevant to humans, some animal which is sensitive both to radiation and to tobacco smoke would need to be studied, and the design should include a control group exposed to neither, groups exposed only to radiation and only to smoking, and a group exposed to both in varying temporal sequences.

18. Experimental studies could be particularly useful for deriving an appropriate model of exposure-time-response relationships for short and long-lived radionuclides. This would involve comparisons of the effects of varying age of exposure, duration and dose rate. These results could be invaluable for choosing between alternative models for projecting epidemiological risk estimates beyond the end of follow-up.

19. Further studies of the genetic effects of internally deposited alpha emitters would also be desirable.

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APPENDIX A

DOSE UNITS - RADS, REMS, GREYS AND SIVERTS

X-rays were discovered by Roentgen in 1895, and a few months later radioactivity was discovered by Becquerel. Very quickly the value of x-rays in medical practice was being exploited, but also very quickly came the realisation that harmful effects could be produced. The first case of radiation injury was probably reported less than a month after Roentgen's discovery. within a year radiation-induced dermatitis, eye smarting and epilation was noted, and most human effects now known were seen within a decade. Methods of measuring these rays, of great benefit and of potential risk, were clearly needed.

The X-rays initially used were relatively low energy and therefore of low penetrating power. Their effects were then primarily on the skin and tissues just below the skin. a reddening of the skin, or erythema, was a noticeable biological effect of x-radiation (just as it is of solar radiation). This biological effect was used as a measure of dose received. Although, as a real biological effect, it is in one sense a very good type of dosimeter - no translation need be made from physical numbers to presumed effects on an individual - it suffers scientifically from significant biological variation from individual to individual, and much more importantly, a dose is only measurable *after* some biological effect has been noted.

Some starts were made on international standards of radiation dose in the second decade of the present century, but due to the First World War, it was not until 1925 that formal action resulted. In that year there was held the 1st International Congress of Radiology (ICR). It discussed units, and set up an International Commission on Radiological Units and Measurements (ICRU). At the 2nd ICR, in 1928, the International x-ray and Radium Protection Commission, later called the International Commission on Radiological Protection (ICRP), was established. The ICRP has since then been in the forefront of the definition of radiation problems and the recommendation of dose limitations.

The 1928 ICR also took the major step of defining a reproducible unit of radiation, the Roentgen. This unit has since then had some slight redefinition, and now is defined as: *One Roentgen is an exposure dose of x- or gamma rays such that the associated corpuscular emission per 0.001293 grams of air* (1 cc at 0°C and 760 mmHg) *produces in air ions carrying 1 electro-static unit of charge of either sign* (i.e. 2×10^{-10} Coulombs).

It should be noted that the roentgen as now used is a measure of exposure, not of absorbed dose. It is a measure of the *ability* of a radiation beam to produce ionisation in air, rather than a measure of the energy deposited in any actual amount of material - thus one believes that the radiation field is so many roentgens per unit of time at a place even when there is nothing there by which to measure it or indeed nothing there with which the beam can interact.

This distinction between a measure of exposure and a measure of energy deposited was not clear in earlier days and indeed from a practical standpoint was not important. Thus the Roentgen was used (and, improperly, still is) as a measure of energy deposited or absorbed dose. [At low energies (<2 MeV) the ionisation produced by radiation all occurs very close to the path of the ray itself. If the energy be deposited in the same 1 cc of air to which the Roentgen refers there is no problem in relating ionisation and energy deposited. But above 2 MeV the ionisation and the absorbed energy are more spread out, and measure of ionisation in 1 cc is probably not a measure of total energy deposited.] Another major difficulty about such a dual use is that the radiation which will produce a certain amount of ionisation in air (and thus deposit a certain amount of energy per gram of air) will deposit different amounts of energy in different materials (per gram), dependent on the absorption cross-sections and densities of the materials. In air an exposure of 1 R results in a deposition of energy of 88 ergs per gram of air (88×10^4 j/kg) whereas over a wide energy range the same 1 R results in the deposition of about 95 ergs in one gram of soft tissue while in bone the deposition could (depending on the energy of the x- or gamma rays) be four times higher.

As it would appear very likely that biological effects of radiation would be dependent on the energy deposited in tissue, the roentgen by itself is not a sufficient method of parameterising radiation dose. Also, by its very definition, the roentgen was only useable for x and γ radiation, and not for alpha rays or neutrons.

In 1953, therefore, the ICRU accepted the rad(r) as the unit of absorbed dose - the rad is an energy absorption of 100 ergs per gram. In this definition there is no limitation in the type of radiation producing the absorbed dose nor on the type of absorbing material. Clearly it is a "physical" unit, just as the roentgen is - there is no mention of biological effect.

It is clear from the definitions that 1 R will result, in air, in an absorption dose of 0.88 r, and in soft tissue, in a dose of just less than 1 rad. This near correspondence (obviously not fortuitous) make it possible for radiation fields, measured by ionisation chambers in roentgens per hour, to be immediately translated into rads per hour (in soft tissue); but has also had the effect of maintaining the confusion between exposure dose and absorbed dose.

with the same intent of defining a unit of absorbed dose, but in keeping with the move to SI units, the ICRU defined the gray (gy) - the gray is an energy absorption of 1 joule/kilogram. Then 100 rads = 1 Gy, 1 rad = 1cGy.

Although the definition of absorbed dose clearly widened the scope of radiation dosimetry, opening it up to α and β rays and neutrons, it introduced another complication, in that the same deposition of energy by different types of radiations does not necessarily (and indeed generally does not) lead to the same biological effect. in particular, the same amount of energy deposited in a gram of material (and, a fortiori, in 1 kilogram) by a densely ionising particle such as an alpha ray does not generally produce the same biological effect as the same amount of energy dispersed over a wider volume, as happens with beta rays.

In radiobiological experiments it is possible to determine the absorbed dose produced by radiation of type z, let us say r_z, which causes a certain biological effect, Ω, and compare this with the dose, r_x, of X or gamma rays which will produce exactly the same biological effect. Then a Relative Biological Effectiveness, RBE, can be defined by

$(\mathrm{RBE})_{\omega,z} = r_x/r_z$ where the suffixes Ω and z have been attached to emphasize that this RBE so defined is specific for the particular biological effect and the type of radiation - and in this context neutrons of two different energies will constitute two different types.

For health physics, dealing with human populations, such radiobiological experiments cannot be carried out. To a first approximation, however, it is found in radiobiological experiments that RBE depends on the microscopic deposition of energy - that is, not just on the joules per kilogram but on the linear energy transfer, (LET), the energy deposited along each micrometer of an ionising particle's track. Using this (admittedly far from perfect) correlation, the ICRP adopted the use of the term Quality Factor, Q, which is related to LET as shown in Table A.1, and which acts as a multiplier of the physical absorbed dose to give a unit which is one of biologically equivalent dose. It is further considered (ICRP77) that there may be a further modifying factor or factors introduced by dose rate or inhomogeneity of distribution of radiation dose (the gray is a macro unit, the LET looks at the individual ray, while a distribution factor looks at, for instance, the inhomogeneous distribution of alpha-active nuclei in a tissue); with the addition of this Modifying Factor N the definition of dose equivalent, measured in units of rems, is H(rems) = Absorbed dose (rads) × Q × N. If Q and N are properly known, then a certain dose equivalent produced by one type of ionising radiation has exactly the same biological effect as that produced by any other type (a rem is a rem is a rem ...).

In SI units, the dose equivalent is measured in sieverts (Sv)

$$H\ (Sv) = D(Gy) \times Q \times N.$$

The Q and N, pure numbers, do not alter with the change of units. At present, ICRP assigns the value of 1 to N.

For some particular cases, for instance those of internal alpha emitters, the relationship between the intake of radioisotope and dose received by critical organs (e.g. bone or lung) has not been clear. In these cases it has been usual to parametrise the doses by either the activity retained in the body or by the alpha activity of air taken in by the body. The dose limitations set by various authorities are discussed in the next two appendices - in terms of rems (sieverts) and of microcuries of retained activity in Appendix B and in terms of alpha activity of air and potential alpha energy in that air in Appendices C and D.

Reference

ICRP77. Annals of the ICRP 1, #3, 1977.

TABLE A.1

LET (in water) keV/ μm	Q	Type of Radiation
≤ 3.5	1	X, γ, β
~ 7	2	
~ 23	5	
~ 53	10	fast neutrons, protons
≥ 175	20	α

APPENDIX B

DOSE LIMITATION IN REMS AND MICRO-CURIES

As noted in Appendix A, x-rays were quickly found to be potentially harmful, and the production of erythema was used as a biological dosimeter. The dose to produce erythema was called the threshold erythema dose (TED). Not until 1925, however, does a quantitative recommendation of a dose limitation seem to have been made. In that year both Sievert (Si25) and Mutscheller (Mu26) made estimates of "acceptable" or "tolerable" yearly dose limits. The arguments of Mutscheller were based on observations of x-ray operators who, over the period of a year, received the order of a dose which, given acutely, would produce reddening of the skin, that is a Threshold Erythema Dose, or 1 TED. No biological effects were observed in these persons. He then made the judgement that if 1 TED/yr produced no noticeable effect, one tenth of a TED per year would certainly be tolerable. Sievert's conclusion, surprisingly enough the same with respect to an acceptable yearly dose, was based on measurements of natural background.

With the development of the concept of the roentgen, attempts were made to measure the TED in terms of R. Unfortunately two different methods were used to measure the ionisation - either close to the skin, in which case backscattering from the skin increases the ionisation and thus the R value, or in free air. The European procedure, the first above, gave a value of about 1300 R = 1 TED, the second, the USA method, gave about 550 R = 1 TED. Both values had large errors on them (e.g. 400 - 550 - 650). Taking 0.1 TED/yr as tolerable, the daily figure then becomes either 0.2 R/day (130 rounded down to 100, 365 days rounded up to 400, 0.25 rounded down to 0.2), as suggested by ICRP (Radiology 26: 682 1936) or 0.1 R/day (55 rounded to 50, 365 to 400, and 0.125 rounded down to 0.1 R/day). It is of interest to note that, although the number differed because of the different methods of measurement, the ICRP and the (US) National Committee on Radiation Protection both in fact agreed on the same actual level (within the errors of measurement).

The introduction in the late 1930s and in the forties of new sources of radiation, such as neutrons, fission products and high energy gamma rays from nuclear accelerators, rendered the use of the roentgen no longer appropriate. In its place the rem has since been used (and now the sievert). At the same time the number of persons using radiation was rapidly increasing, and the range of individual biological idiosyncrasy correspondingly increasing. Partly to cope with this, the permissible dose for workers was reduced in 1949 in the USA to 0.3 rem/week. (La80).

In 1956 ICRP (ICRP58) set the average external occupational exposure at 5 rem/yr, or 0.1 rem/wk. The purpose of reducing the level "was to lessen the possible incidence of certain types of somatic damage, e.g., radiation induced leukemia and shortening of life span, which are considered to result primarily from total body exposure".

Bomb testing in the 1950's attracted much public attention to the possible long term effects of low doses of radiation including late somatic effects and genetic effects, as now very large numbers of persons were being exposed to what looked like increasing amounts of radiation. Clearly no scientific evidence exists for genetic effects of radiation on humans (it is of interest that the time often spoken of as being characteristic for establishing a new equilibrium level of genetic effect as a result of a change in radiation level changing the mutation rate, 30 generations, is equal to that since the Norman Conquest of England). Nevertheless, some judgement had to be made about limitation of dose to populations, whereas previously only workers had been involved and only somatic effects considered. The judgement of ICRP in 1958 (ICRP59) was that the limit on the genetic dose (i.e., gonadal dose or dose to the total body) to workers would be 5 rem/yr, with a total of 5 (N-18) rems where N is the age of the individual; if work began before age 18, the total dose to age 30 should not exceed 60 rem. For members of the general public, it was "tentatively" offered for guidance that the average genetic dose to a population should not exceed 2 rem to age 30 years from man made radiation (excluding medical exposures). This is a factor of 30 below the maximum allowed for workers.

ICRP (59) also gives values for particular organs - 5 rem/yr for the whole body or gonads, but 15 rem per year for any single organ except gonads, thyroid or skin; for thyroid and skin the dose should not exceed 30 rem/yr. In more recent recommendations from ICRP (ICRP77), the general principles outlined above (5 rem/yr for the radiation worker) are again confirmed, but put into a somewhat different context. Comparison is made between the accident/fatality rate in industries regarded as "safe" (10^{-4} deaths/man year) and the induction of cancer predicted from dose rates to workers. The ICRP points out further that, on the basis of much experience, a "maximum permitted dose rate" results in a much (ten fold) lower average rate. On the basis of information available on results of radiation the acceptance of a 5 rem/yr maximum will then result in a fatality rate due to radiation which is lower than that taken by society as acceptable in a safe industry. In addition, the 0.5 rem/yr limitation (maximum) figure for a member of the general public would again lead to an average value which would result in fatality rates inside the risk levels society normally accepts for everyday living (in traffic accidents, for instance, death rates in Ontario are 2 $\times 10^{-4}$ per year).

On the other hand, for the general population the ICRP makes no recommendations of any upper limit, on the basis that "continuance of the former genetic dose limit could be regarded as suggesting the acceptability of a higher population exposure than is either necessary or probable." It emphasizes instead that each man-made contribution to dose must be justified in terms of benefit (which should of course outweigh risks).

The ICRP(77) also looks in more detail at exposure to smaller parts of the body. A simple way of doing this would be to consider total grams-rems, or kilograms Sv, the sum of products of doses received by parts of the body and the masses thereof. Such a procedure would imply that all tissues (and all parts thereof) were equally radiosensitive, and it would imply linearity - i.e., that a large dose in a small mass of the body would have the same effect as a small dose to a larger mass; a quadratic dose response function on the other hand would imply that the effects would not be the same. ICRP in fact adopts a somewhat more sophisticated approach. They recommend that dose limitations should be based on "the principle that the risk should be equal whether the whole body is irradiated uniformly or whether there is non-uniform irradiation". A weighting factor w_T is introduced for each major tissue which represents the fraction of the stochastic risk to the whole body (when uniformly irradiated) which is borne by tissue T. Then the effective dose equivalent H_E is given by

$$H_E = \sum_T w_T H_T$$

where H_T is the dose equivalent received by each individual tissue. The 5 rem limitation discussed above then becomes

$$H_E < 5 \text{ rem in any one year, etc.}$$

As an example, w_T for lungs is 0.12; thus if the lung were the only tissue exposed, H_T could be up to 40 rem and the $H_E < 5$ rem limitation would still be met.

It should be noted that the above dose limitations do not include the natural background nor exposure to a patient due to medical diagnostic or therapeutic procedures. For comparison, natural backgrounds are usually in the range of 100 - 200 mr/yr and medical procedures, averaged over the population, between 50 and 100 mr/yr.

For internally absorbed radium, a maximum permissible level was derived in 1941 from observation of persons who had radium burdens. The total was 27 persons with accurately determined body burdens. Twenty, with burdens of 1.2 to 23 μCi showed deleterious effects, while 7, with burden less than 0.5 μCi, had no injuries. On this basis a figure of 0.1 μCi was accepted. Up to the present, with 2000 radium patients studied in the USA alone, no-one with less than 0.1 μCi has been found to have suffered injury which could reasonably be ascribed to the radium.

It should be noted (Ev81) that the levels in the radium burden cases were the levels of residual activity, measured many years after the initial burden, which was probably about 100 times larger. Correspondingly the 0.1 μCi level should apply to residual (long term) activity. As it is applied, however, it is considered a maximum burden; this application builds in a large safety factor of 10-100.

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APPENDIX C

DOSE UNITS AND LIMITATIONS FOR RADON

The roentgen is a physical unit which can, in principle, be applied to any ionisating radiation. The rad again is a physical unit, but in the case of short range particles such as alpha particles, it may require study to determine how many grams of tissue are absorbing the dose. Particularly is this the case if the source of the radiation is internal to the body and/or if it be not certain which tissues are being exposed. It follows that the dose equivalent (rems) is even more difficult to assign.

It was due to these facts that the dosimetry of the alpha emitting radon and thoron and their daughters in mines has followed a more pragmatic route than that met generally in health physics, and the dose limitations introduced reflect this different approach.

The fact that miners on the Erz mountains (of Bohemia and Saxony) often died relatively young with symptoms of lung damage was known to and described by Agricola around 1550 (Ag 56). In 1879 Harting and Hesse proved that the problem in Saxony was primarily one of malignant tumours of the lung (Ha 79).

In Jachymov in Bohemia mining was carried out in 1516 for silver, then sporadically for other metals. In the latter half of the last century U mining began (for use as a stain or dye) and at the turn of the century Ra became a prime target.

The miners of Jachymov suffered from a disease which was called Bergkrankheit or Bergsucht, "mountain disease". Despite the conclusion that the corresponding disease in Saxony was due to malignant tumours, and despite queries to Jachymov from Harting and Hesse, it was not realized that the diseases were the same. The same negative response about lung cancer was received in 1921, and it was not until 1926 that lung cancer in a Ra factory worker was confirmed in Jachymov. More cases were studied in 1928 and 1929. In 1932 Pirchan and Sikl published a paper (Pi 32) concerning 19 miners who died in the period 1929-30. 13 of these had autopsies, and of these 9 had proven pulmonary cancer. The authors discussed possible causes of this abnormally high incidence. Chemical analysis of lung tissue (in one case) gave no evidence of arsenic, Bi, Co, Ni or U. It was suggested that radon was the most probable cause of the tumours (a suggestion that had also been made in 1924 by Ludwig and Lorenser (Lu 24)). The idea at least in part resulted from the similar tumour incidence in the Saxony mines, where again radon was found (but presumably so were many other possible carcinogens) but partly also because the miners "state that discovery of a rich uranium vein is always followed some years later by a strongly increased mortality among them". It is of interest that the average levels of radon were 10 Maché units per litre of air, or approximately

3600 pCi/l (i.e., 36 WL if there is complete equilibrium of daughters) (the Saxony mines were reported to be at 50 Maché units and this value was also found in one Bohemian mine). It is also of interest that the authors suggested that prevention of disease could be obtained by forced fresh air ventilation or the wearing of respiratory filters (with animal charcoal to absorb the radon).

Lange found (La 35) that in Schneeberg (Saxony) lung cancer caused 60-70% of all deaths of miners (or ex-miners). It also appeared that cancer incidence was three times higher in regions of high radium content than in other regions.

A summary of "results to date" from Jachymov in 1939 by Peller contained information on the 89 miners and pensioners who died between 1928-1938. Sixty of these had had autopsies, and of these 43 (50% of all deaths or 70% of autopsies) had lung cancer. Twenty four out of 30 who did not die of lung cancer had other lung problems (Pe 39).

Lorenz reviewed all the literature up to 1944 (Lo 44). He noted that radium dial painters did not develop lung cancer (but did get bone sarcoma) although they exhaled radon, and that Belgian radium factory workers had not developed lung cancers although "literally covered with dust... yellow from head to foot and will not wear masks" (yellow presumably from yellow cake, uranium oxide). Nor were ill effects noted in those who worked in radioactive "therapeutic" baths or who drank ("therapeutically") radon-containing water. [However it was known that drinking radium water could be dangerous (Ge 33)]. On these grounds, and on grounds of animal data, he concluded that "the opinion that radon is the sole cause of lung cancer of the miners therefore cannot be maintained". He cited other possible contributory factors, including genetic susceptibility.

In 1940 Evans and Goodman reckoned that the Erz mountain miners had been exposed to radon concentrations of about 3000 pCi/l (Ev 40). On the basis of a large margin of safety, they recommended a safe working concentration of 10 pCi/l. This was accepted by the US x-ray and Radium Protection Committee in 1941 (NBS 41). In 1943 the corresponding UK committee accepted 100 pCI/l, but in 1948 reduced this to 50 pCI/l (which, see later, may have influenced by Mitchell's estimate in 1945).

In 1945 Mitchell estimated that the radon concentration in the Erz mountain mines was about 15,000 pCi/l. Knowing the incidence of lung cancer, and assuming a linear dose-effect relationship, he reckoned that radon would have to be reduced to a concentration of 50 pCI/l in order that the incidence of cancer in the miners did not exceed the average rate in the general population (Mi 45).

At this same time Mitchell made an important contribution when he suggested a reason for the known fact that the majority of the lung carcinomas in the miners were of the large bronchi. This may be due to the fact that the ratio of the volume of a regular geometric body to its surface area increases linearly with its dimensions. If then the activity is proportional to volume of inhaled air in a vessel, and if all this activity is "plated-off", the activity/area will go up with radius, and the dose will similarly increase if the effective thickness of tissue exposed is a constant (a reasonable assumption as this will be governed by the range of the alpha particles themselves). Thus the dose will be large in the large vessels.

In 1951 an informal meeting of scientists in Salt Lake City discussed problems of health physics in U mines. No definite conclusions were reached. One suggestion was that the maximum allowed radon concentration should be 1000 pCi/l, with strong efforts to reduce the concentrations to as low a level as possible. Another view was that total alpha radiation should not exceed 1000 pCi/l (a somewhat improper use of the term Curie), with dust content kept at a low level - and that under these conditions no serious hazard would exist. 1000 pCi/l of alphas is roughly the same as 300 pCI/l of radon in equilibrium with its short lived daughters. (Actually freeing the air of condensation nuclei might well increase the dose to the upper respiratory tract).

In 1953 the US NCRP accepted a Maximum Permissible Concentration in air for radon-222 of 10 pCi/l for continuous occupational exposure (NBS 53).

A meeting in 1953 of scientists from the USA, UK and Canada held a majority view that 100 pCI/l of radon "including equilibrium dust" should be the $(MPC)_{air}$. Morgan continued to feel that 10 pCi/l was a better figure (Ar 53 and Mo 54).

It was in fact not until 1951 that it was recognized (Ba 51) that the radon daughters trapped in the lungs were the chief causes of dose - this is because the radon itself, an inert gas, is breathed in and out, while the short-lived daughters - Po, Pb and Bi - may be trapped in the lungs and may be built up over times of the order of their half-lives.

Animal experiments started to make it possible to do better calculations on doses to be expected from radon and radon daughter concentrations. They also showed that the free ion RaA fraction was a very potent source of upper respiratory radiation dose. In 1955 Chamberlain and Dyson (Ch 55) concluded that the build up of dose in this region was due in this region was due to RaA (the first radon daughter) which had been formed in the air of the mine and which was still existing as a free ion when it was breathed into the lungs. (It is of interest that perhaps only 10% of the RaA is a typical mine atmosphere is uncombined, and hardly RaB or RaC). The activity attached to dust particles is carried down to, and trapped by, the more distal parts of the lung, and thus this gets a much higher energy deposited in it. The dose however (energy/mass) will be less and, as was noted, the induction of cancer seems less at these sites.

On these animal experiments ICRP based their 1959 recommendations for the $(MPC)_a$ of ^{222}Radon. Their formula, dependent on the fraction f of free RaA ions, was

$$(MPC)_a = \frac{3000}{1 + 1000f} \text{ pCi/l.}$$

If f is zero (i.e. no free ions), this reduces to 3000 pCi/l, a value estimated by Morgan (1954) to give a dose-rate of 300 mrem/wk to the main bronchi (15 rem/yr was at the time the dose allowed to single organs). On the other hand, with f = 0.1, the value Chamberlain and Dyson felt appropriate for mines, the $(MPC)_a$ becomes 30 pCi/l, which is the value Chamberlain and Dyson felt would give miners 300 mrem/wk to the bronchi (ICRP 59). Table 1 of ICRP 56 then gives the 40 hour week maximum permissible concentration of radon in air as 300 pCI/l (with a footnote that the daughter elements are present to the extent that they occur in unfiltered air), and the 168 hour week value as 10 pci/litre. Correspondingly for thoron (and its daughters) the $(MPC)_A$ was given by ICRP 59 as

$$(MPC)_A = \frac{6,000}{1+40,000f} \text{ pCi/l}$$

where f is here the fraction of ThB which exists as free ions. As f = 1/2000 was regarded as a reasonable value, Table 1 of ICRP 59 gives the $(MPC)_A$ for Thoron as 300 pCi/l (40 hour week) and 100 pCi/l (168 hour week), with the same proviso about daughters.

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APPENDIX D

UNITS FOR RADON DAUGHTERS

D.1 Dose Units and Limitations for Radon Daughters

From the discussion above, it would appear that an ability to measure the ionisation produced in air by the radioactivity in the air (i.e. to measure roentgens) is not the most useful, as the radon component of the total ionisation will be the biggest one (in an area with any ventilation) but probably will biologically be the least important. From this realisation comes the idea of measuring the energy released from the short-lived radon daughters and from this the unit called the Working Level - a person is said to be exposed to 1 Working Level (1 WL) if any combination of the short lived daughters of radon in one litre of the surrounding air will result in the ultimate emission of 1.3×10^5 MeV of alpha particle energy.

1.3×10^5 MeV is in fact the energy that would be released by the short-lived daughters in radioactive equilibrium with 100 pci of radon per litre of air, but there is no requirement that equilibrium must exist. Generally there is no such radioactive equilibrium in a working area; the RaA component will then be greatest and as it is probably the free ionic RaA that contributes most to the biological effect (above), this means that the same WL may, under different ventilation conditions, produce different biological effects. This matter is discussed in Section D.4.

The WL is an exposure rate and is related in a way not yet defined to some dose equivalent rate. The corresponding total exposure is the sum of terms of appropriate working level multiplied by the time spent at that WL. The unit is the Working Level Month, or WLM, where the "month" here is a working month of 170 hours. Being at 1 WL for 12 working months gives a dose of 12 WLM, or at 0.1 WL for 10 working months gives 1 WLM - on the other hand, a person at 1 WL for 12 complete months will receive approximately 52 WLM.

D.2 Radon Daughter Standards in WLM

The maximum permissible concentration in use in the early 1950s, 100 pCi/litre of radon, which was endorsed by ICRP in 1954 and 1955 (ICRP 55), could be construed as endorsing as permissible an exposure of 1 WL, with a corresponding yearly limit of 12 WLM. This limit was accepted by the Ontario Department of Mines in 1957.

After the publication of ICRP #2 in 1959 (ICRP 59) with its radon $(MPC)_a$ of 3×10^3 $(1/(1 + 1000 f))$ pCi/l where f is the fraction of ions unattached to aerosols, reconsideration was given to the Ontario limit. Assuming $f = 0.1$, $(MPC)_a = 30$ pCi/l of radon in equilibrium with its daughters, which then gives a limit of 0.3 WL or 4 WLM/year. It was decided that the Ontario limit be reduced to this over a period of years, and this was done - to 8 WLM in 1973, 6 WLM in 1974 and 4 WLM in 1975.

The regulations adopted for Canada by AECB in the late 1970's permit up to 4 WLM (radon daughters) a year, with a limit of 2 WLM in any one quarter.

It should be noted that to some considerable extent these values are based on judgement using all available epidemiological data. It was realised that in addition to radon exposure, miners also were subject to gamma exposure; but as to a considerable degree in Ontario mines with adequate ventilation these two exposures went hand-in-hand, the 4 WLM limit took into account the concurrent gamma exposure - that is, gamma dose was not added separately. A different approach which is gaining support is to treat the two effects separately, with the total body dose not to exceed the equivalent of 5 rem/yr. Clearly this approach requires a knowledge of the WLM/rem relationship. Assuming a value of 1 WLM/effective rem (but see Appendix E), on this basis the "bare" radon daughter limit would be 5 WLM per year. In Ontario, the gamma/radon daughter ratio is such that the actual allowable radon daughter limit would be 4 WLM (with a further 1 WLM equivalent of dose acceptable from the concurrent gamma dose). This approach must be of greater importance in high grade deposits or in other open pit operations. Using the "reference value" of 0.8 rem/WLM given in Appendix E.2, this "bare" figure of 5 WLM/yr and the Ontario figure would be proportionately increased.

A further approach, which avoids the need for a stated relationship between WLM and rem, lays down that if 5 WLM is the limit for pure radon daughter exposure and 5 rem the limit for pure gamma exposure)

$$\frac{x}{6\ \text{WLM}} + \frac{y}{5\ \text{rem}} < 1$$

where x is the radon daughter exposure in WLM and y the gamma exposure in rem.

In the U.S. the maximum permitted exposure was reduced to 4 WLM per year in 1971. An additional support of this value (apart from ICRP) was that over 30 years work in a uranium mine at this maximum, a worker could be exposed to 120 WLM, and the Colorado data available in 1971 (Lu 71) indicated that no excess cancer risk existed at this level.

D.3 WLM as Energy Intake

The WLM may be expressed in terms of potential alpha energy taken into the lungs if a particular breathing rate be assumed. As 1 WL means a potential α energy of 1.3×10^5 MeV per litre, and 1 working month contains 170×60 mins., if the breathing rate be B, then 1 WLM implies an intake of potential α energy of $(1.3 \times 10^5) \times (1.6 \times 10^{-13}) \times (170 \times 60) \times B$ Joules, where the second term is the conversion from MeV to Joules. If B is 20 litres/minute, then 1 WLM is equivalent to 4×10^{-3} J intake and 5 WLM = 2×10^{-2} J.

D.4 Effect of Ventilaton on WLM Dose Relationships

To the total 1.3×10^5 MeV of potential α energy per litre from short-lived daughters (which defines 1 WL), the various daughters contribute differently. RaA contributes most per nucleus, because each (7 MeV) disintegration of RaA is followed later by another (6 MeV) disintegration of its great grand daughter RaC', whereas both RaB and RaC contribute only 6 MeV each. But as the half-life of RaA is only 3 minutes, there are relatively few RaA atoms in each litre (only about 0.09 of the RaB atoms), and so the total contribution of RaA is only one fifth of that of RaB. Taking these facts into consideration, one may write the working level as

$$WL = 0.001\ (\text{pCi}/\ell \text{ of RaA}) + 0.0052\ (\text{pCi}/\ell \text{ RaB}) + 0.038(\text{pCi}/\ell \text{ RaC})$$

(there are so few RaC' atoms that they may be neglected). For 100 pCi/ℓ of each of RaA, RaB, and RaC, then the WL is 1. But for 100 pCi/ℓ of RaA and no RaB or RaC, WL = 0.1. These are both extreme positions, but the actual WL in an area where there is 100 pCi/ℓ of RaA may vary in wide limits. A table adapted from Table 1 of Ha 74 shows possible values. As a high proportion of the dose to the tracheal-bronchial region (up to 90%) is considered to be due to the unattached (to aerosol) fraction of RaA diffusing to the walls of the bronchi, variations in (RaA concentration)/WL by a factor of 10, as above, could also mean the same variation in (Dose)/WL.

The situation could be actually more complicated than this. Brisk ventilation, which would reduce the (RaB and RaC)/(RaA) ratio, would also reduce the aerosol concentration and thereby increase the proportion of free (unattached) ions of RaA. This would further increase the dose per WL, but it must be realised that such a ventilation rate will greatly reduce the RaA itself (as it would also be quickly removed) and so the WL itself would be greatly decreased.

Table D.1
Working levels calculated for 100 pCi/l of RaA
and indicated concentrations of RaB and RaC'.

pCi/l RaB	pCi/l RaC' 100	80	50	30	10	0
100	1.0	0.92	0.81	0.73	0.66	0.62
80		0.82	0.71	0.63	0.56	0.52
50			0.55	0.47	0.40	0.36
30				0.37	0.30	0.26
10					0.19	0.15
						0.10

References

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APPENDIX E

LUNG MODELLING

E.1.1 Lung Models and the WLM/rem relationship

When air containing radon and its daughters is inhaled, the radioactive material is also taken in. Some of this radioactive material will decay in the lungs, giving rise to a radiation dose. The fractions that do so decay depend on the chemical and physical properties of the particular elements. Radon, for example, is an inert gas, and therefore does not become attached to body tissue (except by solution in body fluids). For comparison, radon in air at a concentration of 100 pCi/litre will give a specific activity in tissue of 1 Bq/kg while potassium-40 exists in the body at a specific activity of 70 Bq/kg. The daughters can however become attached to material; such attachment may be to dust particles before entering the lungs. There is then the possibility of these aerosols being deposited and retained on lung tissue; or the daughters may exist as free ions (or in the form of small molecules, Bu 81) which may then become deposited and retained directly on tissue.

The capture of the ^{222}Rn daughters means that they become concentrated with respect to the amount in the air outside the lungs - the activity will then build up (after starting to breath the contaminated air) over a period whose length is governed by the half-life of the isotope in question. For the first daughter, RaA (^{218}Po), the half-life is 3 minutes and so (to a first approximation, and assuming complete capture) the activity of RaA in the lungs becomes greater than that of radon by an amount equal to the number of breaths taken in (3/0.693) minutes. For this reason the dose received from radon itself is almost negligible (30 μrem/hr for 100 pCi/litre) compared with that from the daughters (particularly in the region of potentially greatest interest from a carcinogenic point of view) and will be only briefly mentioned here.

Autopsy and other studies indicate that the principal site of (lung) cancer in uranium miners has been in the upper bronchial region (rather than, for instance, more distally, in the alveolae). In so far as this is connected with radiation derived from the air in the mines, it must also reflect some deposition and/or retention of the radioactive material in this bronchial region. The physical state of attachment of the radon daughters to aerosols is found to be an important factor in determining their site of deposition and their fate once deposited. This is because daughters in an ionic state are more free to diffuse to the walls of the air pipes in the lungs than are the heavier attached atoms or (the reverse side of the coin) the aerosols are more likely to be carried by inertia into the more distal parts of the lungs. Once deposited on lung tissue surface, the atoms and dust particles may be treated like any other material - the material may be dissolved and go to blood, may be removed by ciliary or other mechanical action to the GI tract, or may go to lymph.

To improve understanding of the above processes, and to make possible some (better than zero order) calculation of dose to various parts of the lung resulting from intake of air containing radon daughters, lung models have been proposed and examined by various authors.

E.1.2 Lung Models

All models divide the respiratory system into regions such as nasal, pharyngeal, tracheal, bronchial and pulmonary. Partly because of the major site of radiation induced lung cancer, there have been sub-divisions of the bronchial part of the above system into different regions. Landahl (La 50) considered a subdivision into 6 generations of bronchi, Weibel (We 63) considered 16 generations, while ICRP (ICRP 75) prefers a lung model devised by Horsfield and Cumming (Ho68) with 5 lobar bronchi and 19 segmental bronchi. The differences between these last models are about ±25% in total surface area and volume. As the thickness of tissue irradiated has an upper limit set by the range of α particles, the surface area is very important in determining total mass exposed and therefore dose - and similarly volume has implications for the amount of radioactive material present which can be deposited on the surface. As however the ICRP model has, compared to Weibel's, both lower area and lower volume, the effects tend to cancel out in the estimation of dose.

The ICRP committees have developed a lung model which takes into consideration not only deposition but also removal to body fluids (BF) or the GI tract. Diagrams 5.1 and 5.2 of ICRP #30 (ICRP 79) show the main features - three main areas, the nasal-pharyngeal (N-P), the tracheal-bronchial (T-B) and the pulmonary (P). Deposition in each of these depends on aerosol size, and diagram 5.1 of the volume cited shows the variation of deposition with mean diameter. In the T-B region the deposition differs little however over the range of diameter 0.2 to 10 μm. From each of the three areas a fraction of the amount deposited may go to body fluids (BF) or the GI tract with a characteristic biological half-life. The respective fractions and the half-lives depend on the chemical properties of the aerosols, and materials are all classified into three groups, those that would be removed from the lungs in roughly days (D group), weeks (W) or years (Y). From the pulmonary region, in addition to the removal rates to BF or GI, there are additionally the possibilities of translocation by mucus to the T-B region or removal to lymph nodes (whence there may be further removal to BF). All kinetics are assumed to be first order.

E.1.3 Deposition

After deciding to accept a particular model, it is then possible to proceed to the next step, that of estimating the percentage of particles (free ions and/or aerosols) which are deposited per unit area of the air passage. Such a calculation depends on diffusion coefficients, aerosol size and rate of intake of air. Some of these matters will be taken up in more detail later in this Appendix. Under mine working conditions, the surface deposition probabilities seem to peak in the lobar bronchi or segmented bronchi regions. For the larger diameter aerosols (around 0.3μm diameter), inertial impact is the dominating cause of deposition, whereas with smaller aerosols (0.1 μm), and with free ions, diffusion is the dominant term. These conclusions are taken from James (Ja 81) but are in general agreement with work of Jacobi (Ja 80) and Harley (Ha 72) and with experimental findings (Ge 69, Li 77). To a first approximation some 30% of radon daughters entering the trachea may be deposited on the lobar and segmental bronchi and another 15% in the transitional bronchi.

These radioactive particles will in fact be deposited on mucus which covers the cellular tissue. The mucus is being moved by cilia, and there is a possibility that the radioactive material will be transported from the bronchial region (to the GI tract for removal) before α-decay takes place. However, other radioactive material will be being moved into the region of interest from more distal parts of the respiratory system. Rates of mucus transport in the region of interest are of the order of 0.1 cm/minute, so that RaA nuclei will only be moved a short distance before decaying.

E.1.4 A First Order Calculation

A first order calculation may be helpful at this time. Let us assume an atmosphere containing 100 pCi of radon daughters all in equilibrium per litre of air; that 10% of the RaA exists as free ions and that breathing is at the rate of 20 litres per minute. Then, following values given by James, (Ja 81) and Jacobi (Ja 80), the surface deposition probability in this area is $2 \times 10^{-3}/\mathrm{cm}^2$ for the (0.1) fraction of free RaA ions, and $2 \times 10^{-5}/\mathrm{cm}^2$ for the (0.9) fraction of aerosol-attached RaA. One then gets (20×100) pCi/min $\times$ $(2 \times 10^{-3} \times 0.1 + 1.8 \times 10^{-5})\ \mathrm{cm}^{-2} = 0.44$ pCi/min $\times$ cm^2). Now RaA is built up over a mean time of 3 min/0.693, (as the half-life is 3 min) so that the equilibrium amount deposited will be 2 pCi/cm^2. Each decay of RaA gives rise to (6 + 7.7) MeV of α radiation; the range of the α rays is 50 μm; on average about half the rays will be going into the tissue and half will be going the "wrong way" and may be "lost". Then the dose will be (remembering mass = 50 μm × unit area × unit density)

$$\frac{(2 \times 3.7 \times 10^{-2}\mathrm{Bq}) \times (13.7 \times 1.6 \times 10^{-6}) \times 3600 \times 10^{3}\ \mathrm{mr/hr}}{50 \times 10^{-4} \times 100 \times 2}$$

= 6 mrad/hr
→120 mrem/hr taking $Q=20$
=240 rem/working year of 2000 hrs.

Now must be added in the effect of RaB and RaC. These will be almost entirely on aerosols, and therefore only little absorbed in this region; but as RaB has 10 times the half-life of RaA (and RaC 6 times), and as the α energy available from each is one half that from RaA (and its daughters), to a first approximation RaB contributes a further 120 rem/yr and RaC 60 rem/yr, giving 420 rems for 12 WLM or approximately 33 rems/WLM (the beta ray equivalent dose is neglected because of its unity quality factor, very small compared to the 20 for the alpha particle).

This above calculation is designed simply to serve as a guide to more detailed calculations and as reference to corrections to this simple picture which should be made because of factors left out or crudely estimated. For instance, a Working level does not have to have equilibrium levels of RaA, B and C, and in general does not (see Appendix D). But as RaA (on this picture) provides more than half the dose, a disequilibrium tilted towards RaA (the usual pattern produced by ventilation) will produce an equivalent dose per WLM greater than the 33 rems calculated above. Again, the simple picture takes no account of transport of the active materials nor, more importantly, does it consider the absorptive effective of the mucus layer on the windpipe surfaces. It does however note the importance of knowledge of the number of breaths per minute, of deposition probability and, implicitly, of the ratios of RaA, B and C in the inhaled air. For thoron daughters similar calculations can be made.

E.1.5 More Detailed Calculations

More detailed calculations relating the equivalent dose to the WLM have been made by various authors. The spread of estimated values has been 5-150 rem/WLM in the period 1964-1972 (the above calculations are in this range), but more recent detailed estimates have been in the range 2-20 rem/WLM. Jacobi and Eisfeld (Ja 80) for instance calculate that the average equivalent dose (Sieverts) to the basal cells of the tracheal-bronchial region (TB) can be written

(1)
$$\overline{H}_{\text{TB-Basal Cells}}/I = 18(1+9f_{\text{pot}})$$

where F_{pot} is the unattached fraction of the total potential alpha energy of the daughter mixture and I the potential energy in Joules.

Somewhat earlier, Jacobi (Ja 72, Ja 75) used the ICRP lung model and class D clearance is calculated dose to the TB region:

(2) $$\overline{H}_{\text{TB}} = 15(1+6.7f_{\text{pot}})\text{Sv/J}.$$

The two calculations are slightly different, but it should be noted that the first refers to dose to the basal cells, whereas the second is averaged over the 0.045 kg of the TB region.

In the pulmonary (P) region the corresponding relations are

(3)
$$\overline{H}_P = 5.2(1-f_{pot})\ \mathrm{Sv/J}$$

and

(4)
$$\overline{H}_P = 7.7(1-f_{pot})\ \mathrm{Sv/J}$$

for the two calculations (Ja 80 and Ja 72). The difference here results from different assumptions of the deposition probabilities in the P regions.

These relations can be expressed in terms of WLM (rather than J) with an assumed breathing rate. Taking this as 1.2 m³/hour, the 4 relations become

(1) $\overline{H}_{TB-BC} = 7.3(1+9f_{pot})$ - range 7.3 → 13.9

(2) $\overline{H}_{TB} = 6.2(16f_{pot})$ - 6.2 → 9.9

(3) $\overline{H}_P = 2.2(1-f_{pot})$ - 2.2 → 2.0

(4) $\overline{H}_P = 3.2(1-f_{pot})$ - 3.2 → 2.9

in units of rem/WLM where the range of values indicated is for $f=0$ to $f=0.1$.

Other recent calculations (Ja 81a) gives a range of dose to the bronchial stem cells of from 6 rem/WLM (high dust loading of the air) to 20 rem/WLM (high ventilation, clean air). Dose to alveolar tissue is calculated to be 5-10 times less than this (1-2 rem/WLM).

E.2 Tissue Weighting

The ICRP has now adopted (ICRP 77) the concept of an "effective dose equivalent", H_E, the summation of dose equivalents to different tissues multiplied by, for each of the tissues, a weighting factor w_T which represents the "ratio of the stochastic risk resulting from tissue T to the total risk when the whole body is irradiated uniformly". Then $H_E = \sum_T w_T H_T$ where H_T is the mean dose equivalent in tissue T.

The question now arises as to the weighting of lung and of parts of the lung. ICRP has suggested a value for the lung as a whole of 0.12. Using this, and the values of total lung, a Mean Lung Dose (MLD) results (a dose from the "mean lung"). On the other hand, the lung can be regarded as split into two parts (TB + P) for dose calculation purposes, each of $w_T = 0.06$: this then gives a Regional Lung Dose (RLD) approach. Because of the very different dose equivalents per inhaled joule of α energy in the two (TB and P) regions, the two approaches give different values. In the range of f values 0-0.1, the expected values in mines, and encompassing the differences between the Jacobi (Ja 80) and the ICRP lung models, the MLD approach gives 0.35 (f=0, Jacobi) to 0.5 (f=0.1, ICRP) effective rem per WLM, while the RLD gives 0.6 (f=0, ICRP) to 1.0 (f=0.1, Jacobi) effective rem per WLM. The calculations of James et al. (Ja 81a) gives a range of 0.6-1.0 effective rem per WLM, with 0.8 suggested as a reference value.

To get the full effective equivalent dose the (weighted) doses to other tissues should be added. Because of the short half-lives of radon daughters, this additional term is very small (less than 10%), and may be neglected here.

In concluding this section, reference should be made to the corresponding calculations for thoron and its daughters discussed in E.5. The nuclear half-lives of the thoron daughters, quite different from those of the radon daughters, makes many differences - for instance, referring to the last paragraph, doses to other tissues cannot be neglected.

E.3 Annual Dose Limits

E.3.1 Use of Lung Models

From the above values it is but a step to suggest maximum exposures based on the overall ICRP recommendations of 5 effective rem per year per worker. The highest value would be 5/0.4 = 13 WLM, which would only be applicable to old air with RaA completely attached to aerosols (f=0), while the most conservative (for the range of f=0 to 0.1) would be 5/1.1 or 5 WLM.

These values would then lead to an exposure rate limit of 13 WLM/12 m =1 WL or, more conservatively, using f=0.1 and the Jacobi model, 0.4 WL.

E.3.2 Epidemiology Approach

An other approach, utilising epidemiological data on risks associated with α-radiation, is to accept that the risks to miners from radiation should not be greater than that of other workers using radiation. This latter is taken, by reference to mortality rates in "safe" industries, as 1 death per year per 10,000 workers or 10^{-4}/yr. This, (ICRP 77 (par. 60))is the risk rate expected from all cancer deaths from an average effective dose equivalent of 1 rem per year. As an example, assume that the mortality rate for radiation-induced cancer is 10^{-4} per WLM; then as under this assumption 1 WLM produces the same risk as 1 effective rem, 1 WLM could be equated in risk to 1 effective rem if, on the other hand, the mortality rate is assumed to be 5×10^{-4}/WLM, then 1 WLM can be equated in risk to 5 effective rem and an annual dose limit of 1 WLM would be appropriate.

Maximum permissible WLM/year values based on the above figures may be compared to the current value of 4 WLM/year (see Appendix D).

E.4 Factors Affecting Dose to the Lung

E.4.1 Effects of Mucus on Transport and Absorption

Mucus on the surfaces of lung airways is moved upward by ciliary action, so that particles in the mucus may be finally swallowed. The process of removal may take minutes to hours. The rate of flow is around 1 cm per minute at the top of the bronchi or in the trachea, but falls to one hundredth of this at the bronchioles. With respect to dose to the upper bronchial region, radioactive material deposited there is removed by the mucus action, but on the other hand material deposited more distally is moved upward to the bronchial region and may decay there. To a first approximation material will take so long to get from about the 8th generation of the bronchi splitting to the upper bronchi that the radioactive daughters of radon will have decayed first. This suggests that changes in ciliary clearance times will be relatively unimportant. Acute exposures to tobacco smoke have been observed to increase the rate of ciliary clearance, (Ho 69) whereas chronic exposure has been observed to have the opposite effect (Lo 71).

The thickness of the mucus will have an effect on α-absorption. The layer is generally about 7 μm thick, sufficient to absorb somewhat less than 20% of the α-ray energy. Changes in this thickness can therefore cause dose changes of perhaps up to 10% per WLM.

E.4.2 Effect of Epithelial Thickness on Dose

The cells at most carcinogenic risk in the airways appear to be the basal stem cells of the epithelium of the bronchi. This may be due to a larger turnover of epithelial cells due to viral infections (which will require these stem cells to proliferate more rapidly than other cells more distal). These viruses may themselves act as "keys" in the supposed pathways of carcinogenesis. Irritation by non-viral entities, for example pollen and smoke, may also result in more rapid loss of bronchial epithelial cells.

The basal cells themselves will not be in direct contact with radon daughters (unless they are absorbed by the blood, a small probability) and the epithelial cells will act as a shield. According to Ga 72 the thickness of the epithelial cells varies in different parts of the pulmonary system. In the lobar and segmental bronchi the mean thickness is about 55 μm (sufficient to stop an α particle), but as the distribution about this mean is wide (± >50%) a significant fraction of the α rays can penetrate to the basal layers, giving a dose which is however less (perhaps a half or a third) of what it might otherwise be. The most sophisticated calculations have been done by Harley and Pasternack (Ha 72 and Ha 73). In more detail they predict the general conclusions reached above.

E.4.3 Factors Influencing the Unattached Fraction

As there is evidence that the fraction of radon daughters unattached to aerosols contributes greatly to dose, the question of the fraction of unattached ions is one of great importance. Factors which influence it include:

E.4.3.1 Particulate concentration.

Porstendorfer et al. (Po 78) found that the half-life for attachment decreased from 60 seconds at particulate concentrations of 2×10^4/mℓ to about 14 seconds at 7×10^4/mℓ - with a half-life of 15 seconds for attachment, one would expect less than 5% to be unattached. In mines, concentrations of aerosols are likely to be in this range.

A variety of authors (reviewed by George et al. (Ge 75) have concluded that with particle concentrations less than 10^4/mℓ the uncombined fraction is in the region of 30-40%. By 2 or 4×10^4/mℓ, f is down to 10%, and by 10^5 to 5%.

In modern mines, operated with diesel equipment, a reasonable mean value for f the unattached fraction would seem to be 4%, but with a range from 0.4 to 16% (Ge 75).

E.4.3.2 Aerosol Size

Jacobi (Ja 72) has derived a formula for the rate constant for the attachment of free radon daughter atoms to aerosols which is

$$\lambda_a(\mathrm{hr}^{-1}) \approx 0.06\ \delta\ D^{1.3}\ N$$

where D is the Count Median Aerodynamic Diameter and the geometric standard deviations of the size distribution is δ: N is the number of particles/mℓ. Under active mine conditions λ_a may be in the range 500-2000 hr^{-1}, that is the half-life for attachment may be 15 seconds to 1 minute.

E.4.3.3 Humidity

With increasing humidity of the air, aerosols probably increase in size, and there is an increase in the rate of attachment of ions to the aerosols (Po 78). On the other hand, there is dispute as to whether increase in humidity increases or decreases the diffusion coefficient of free ions. Raabe found a decrease in the coefficient with increased humidity, whereas others have found the opposite (Ra 68, Po 68, Ko 76, Th 70).

Porstendorfer and Mercer (Po 79) concluded that in the range of relative humidity 30% - 90% there was no great change in the diffusion coefficient, but that in very dry air the coefficient decreased.

E.4.4 Aerosol Size and Deposition of Activity

The size of aerosol to which radon daughters are attached markedly affects the rate of deposition of the dust particles in all parts of the lung system.

Most noticeably, large particles (> a few μm) are trapped in the nasal passages or the pharynx. On the other hand with small size (0.5 μm) the majority of aerosols go right through to the pulmonary region.

The typical size of aerosols in modern mines is taken to be around 0.1 to 0.5 μm. As noted there is little filtration by the nose at these levels and therefore whether breathing is by nose or mouth makes little difference. For both the pulmonary and the tracheal-bronchial regions deposition is increasing as aerosol size falls. Different lung models result in differences in calculated values of these effects. One, for instance, predicts that between 0.5 μm and 0.1 μ there is about a two- or three-fold increase in deposition in the T-B region (ICRP Task group on Lung Models, quoted in Brain and Vallberg (Br 74). Correspondingly the dose will increase as aerosol size decreases.

This conclusion is only in fair agreement with the calculations of James (Ja 81, Ja 81a). He shows that in the bronchioles a change from early-U-mine conditions (0.1 μm) to modern conditions (0.3 μm aerosol size) can double the dose to the bronchioles, but that the increase in size due to the physiological high humidity may alter these conclusions.

E.4.5 Effects of Breathing Rates on Dose

If a hard worker is taking more air into his lungs every minute than another person breathing the same air, he will take in more radioactivity. To a first approximation, he would be expected to have more deposited in the bronchial region and thus a higher dose. There are however second order effects which depend for instance on aerosol size. It can be appreciated that the air in each breath is moving more quickly with rapid breathing, and so aerosols have less time to diffuse to the walls of a bronchial air way. The other side of this is that the particles will have a higher inertia (momentum) and so will more possibly hit bifurcations of the airways rather than "streamline" past them.

Shapiro (Sh 56) found that the percentage retention of daughter product from uncleaned air varied linearly with tidal volume between 0.7 and 1.5 litres (from 22 to 30% retention). He also noted that, with cleaned air, retention at 1.5 ℓ tidal-volume was about 75%.

James (Ja 81) states that in modern U mines the dose to the upper bronchial tract can vary by factors of 2 or 3 depending on whether the miner is breathing at a heavy or a moderate rate. However in a later paper (Ja 81a) it is considered that a mean breathing rate of 20 litres/minute is appropriate both for underground and open pit miners.

E.5 Thoron and the WLM/rem Relationship

The Working Level (WL) and the Working Level Month (WLM) are defined in terms of potential alpha energy and apply to both radon and thoron. However, because of the different nuclear properties of radon and thoron daughters, the dose produced in the lungs by exposure to 1 WLm from Thoron or radon would not be expected to be the same.

At the outset, it may be remarked that although the WL came about by reference to 100 pCi/l of radon in equilibrium with its short lived daughters, for thoron, 1 WL is the equivalent of 7.3 pCi/litre of thoron in equilibrium with short lived daughters. This is largely because of the 10.6 hr half-life of ThB, which results in there being a large number of ThB nuclei per picocurie, and therefore a large amount of potential α energy per picocurie.

The major differences between the dose delivered from Tn and Rn daughters arise from the very short half-life of ThA and the relatively long half life of the overwhelming contributor to the dose, the ThB. It is most likely that the ThB will be on aerosols (rather than as a free ion) and that therefore (on the normal picture of deposition of the daughters) will be carried past the Tracheal-Bronchial region (TB) to the lower, pulmonary (P) region. It is also quite likely that ThB will be removed from the lung before decaying.

Jacobi (1972) calculated that, per WLM, the mean doses to the TB regions are around 0.5 rads/WLM for Rn (range 0.07 to 1.0 depending on aerosol concentration, ventilation, and other considerations) and around 0.01 rads/WLM for Tn (range 0.004 to 0.04) while for the P region the corresponding figures are 0.15 for Rn (0.07 to 0.2) and 0.1 (0.05 to 0.1) for Tn. Thus although the dose to the pulmonary region per WLM is approximately the same for both Rn and Tn daughters, there is more than a 10-fold difference in the corresponding values for the TB region. It will be noted that this factor of ten is of the same order as that between the radon and thoron activities per WL, and as a result, to a first approximation, the dose to the TB region is the same for Tn and Rn at the same activity concentrations (pCi/l). This is not so, however, for the P region, where the dose per pCi/l will be about 10 times higher for Tn than for Tn. Thus in high Tn situations for the same WLM the distribution of lung cancers may be different than in Rn concentrations.

In Ja80 the effect of biological removal of ThB from the lung is made more explicit. The (weighted) effective dose to "other tissues" (other than lung) exceeds the (weighted) effective dose to TB Basal cells for desorption half-lives of less than about 0.2 days (whereas in the case of radon daughters other tissues contributed less than 10% to the total effective dose).

Ja80 calculates dose to TB basal cells from ThA, B and C to be 300, 4.3 and 9.9 Sv/J respectively (for the range of desorption times of 0.2 to 0.5 days). The dose from inhaled ThA under normal conditions is in fact small; in terms of Sv/Bq, the respective figures are 0.016×10^{-8}, 30×10^{-8} and 6.5×10^{-8}. The difference between the Sv/J figures for ThB and ThC are due to biological removal of the ThB from the lung.

For the P dose, Ja80 calculates 2.2 and 4.9 Sv/J for ThB and C respectively (ThA does not contribute significantly in the P region). The dose to the P region is thus about half (per J) the dose to the TB region.

Comparison with the corresponding figures quoted for radon daughters (AE1.5) indicates in the TB region a ten fold greater dose/J from radon than from Tn daughters, with the doses/J being similar in the P region (with Rn daughters giving 1 1/2 to 2 times that of Tn daughters). This agrees with the earlier work (Ja72).

The total effective equivalent dose (to the whole body) is calculated by Ja80 to be (using reasonable parameters of aerosol size, biological removal, etc.) very little different whether the mean or the regional lung concept be used. The value recommended is 0.7 Sv/J or 0.3 rem/WLM. This is very similar to the value for radon daughters, but it must be appreciated that the distribution of this total dose is quite different - almost all in the lungs with Rn, half in other tissue in Tn.

Ja81a gives a table of the dose to different target tissues per unit of inhaled potential alpha energy from thoron daughters in Sv/J. To the TB basal cells the probable range (taking into account uncertainty in biological retention times) is 5-14 Sv/J, to alveolar epithelium 1.4-3.4, to bone surfaces 2-5, 1.2-3.5 to kidneys, and lesser amounts to other tissues. To bone surface, then, the equivalent dose is 1 to 2 rem/WLM (and to bone marrow about 0.1 to 0.2 rem/WLM). The total (weighted) effective equivalent dose given by this compilation is between 0.5 and 1.5 Sv/J (0.2 to 0.6 rem/WLM) for aerosols of size 0.1 to 0.3 µm. A value of 0.4 rem effective dose equivalent per WLM (Tn) is accepted here (as an average of the extreme values above) and correspondingly a value of 0.8 rem/WLM (Rn) is taken, as the "reference value" recommended by Ja81a and as being-again the average value of their ranges.

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APPENDIX F

POPULATION HETEROGENEITY

F.1 Comments on dose-response effects on Population Heterogeneity

In a paper by Baum (Ba73) the question of the effect of a population heterogeneity on dose-response was discussed. In particular, it was shown that if a population contained 1% who were very radio-sensitive ($D_o = 1$ rad) and 10% with a D_o of 100 rads, while the rest had $D_o = \infty$, then, the (cancer) incidence I between 1 rad and 100 rads follows an $I - (\mathrm{Dose})^{0.5}$ law, giving a straight line of slope 0.5 on a log-log plot. It was further pointed out that three strains of Drosophila in fact had different radio-sensitivities. One, with a D_o of 700 r, obeyed one target kinetics and the others, with $D_o > 4000$ r, went more with a 1.6 power of dose. However, as the author points out, the low dose (<1000 r) region is completely dominated by the (linear) low D_o term. Any extrapolation to very low (<100 r) doses based on data in the 100 r region would fully take into account the most radio sensitive group. As the author points out, this linearity is consistent with most human and animal studies. These linearities "are probably all reflecting genetic factors which predispose certain strains and certain organs to cancer". However other strains are not so predisposed and, like the Drosophila data quoted, follow a higher power law, i.e., probably multi-hit target kinetics. Possibly the "predisposition" is a genetic turning of all but one of the keys in the cancer chain which would then make the dose-effect curve linear (assuming radiation were the last key).

In a later paper (Ba75) the same author has elaborated his thesis, considering a model with 5 "keys", each of which has to be turned in order to produce cancer. This sequential process can occur spontaneously. The number 5 is based on a $(\mathrm{time})^5$ relationship between age and cancer (mammary tumor) induction in rats. The time of induction after irradiation with neutrons (at doses of neutrons greater than 18 rads) follows however a different law - more like t^1 in the first 2 years after irradiation, and then t^3 law fits better. A linear law (with time) implies, on the 5 key model, a radiation induced promotion of cells to (key) level 4, but the numbers in level 3 at the time of irradiation can be shown on a Poisson distribution model to be insufficient (even if all were promoted). A simultaneous two-step promotion is therefore called for. The cubic law (above) would similarly follow from a 0-2 level promotion. It is pointed out that a double step could result from the (high LET) neutrons used, as there is a high possibility of multiple ion pair production in any one target area (and it is also pointed out that this is unlikely with gamma rays at low dose rates). For 150, 200, 400 and 600 days post-irradiation, the predictions of the model fit the experimental data well, for doses from 2-250 rads. At short times and low doses (200-400 days, <50 rads) the response curve is linear with dose. At larger times (400 days and 500 days) the corresponding curves follow $D^{0.25}$ and $D^{0.16}$ relationships respectively. However, it is pointed out that if the natural incidence at these longer times be subtracted, "a near linear increase with dose is obtained at small doses (less than about 10 rads)". Thus extrapolation down from 10 rads (100 rems) on a linear basis would appear to be justified in this case also. However, extrapolation on the basis of short time data might under-estimate results.

F.2 Radio-sensitive Diseases

The possibility of sub-linear dose-response curves resulting from fractions of the population being particularly radiosensitive leads to investigations of whether such sub-populations do exist. Some such are discussed below.

There are a number of (rare) diseases in which there have been reports of increased likelihood of cancer incidence and also an increased sensitivity to x-rays. Fanconi's anaemia (FA) and ataxia telangiectasia (AT) are two such.

Both of these diseases are also associated with a high probability of chromosomal aberrations, and this property they share with Bloom's syndrome (BS) and Xeroderma pigmentosum (XP).

FA is a genetic disease associated with an increased risk of leukemia. Several other rare blood diseases are associated with leukemia and chromosomal instability (Sc71). The rarity of the disease is shown by the fact that only 200 descriptions of cases have appeared in the literature. Childhood death is common.

AT (or Louis-Bar syndrome) again is a rare disease, with again about 200 cases referred to. Cancers are more frequent than in the general population and often originate in lymphoid reticular tissue (Pe66). The immune system is disturbed. Data is too sparse to give a detailed picture of chromosomal behaviour, but there appears no doubt about a higher than normal incidence of abnormalities.

Patients with BS have a high risk of cancer (Ge69). In the (only 5) recognised affected individuals whose deaths have been noted, three had leukemia and one another type of cancer.. The fifth died of infection at three months of age. Of the total of 33 persons with the syndrome known and alive, one has leukemia, and all three over the age of 30 have developed at least one cancer of the GI tract. There are marked chromosome aberrations.

XP manifests itself early in life with skin changes consequent on exposure to sunlight; cancers of the skin occur as a result of this (solar) radiation. Chromosomal aberrations are less common than with, e.g. FA.

With respect to radiation sensitivity, there are reports of increased sensitivity of AT patients to x-rays, and radiation survival of cells from AT patients is lower than in the normal population. At 200 rads, roughly only 1% of fibroblasts from AT patients survive as compared to some 30% from normals (Ta75). In contradistinction, cells from patients with basal cell naevus syndrome, which have been shown to have higher than normal spontaneous and x-ray induced chromosome aberrations, showed survivals on a par with normal data.

Taking as a model that for carcinogenesis there must be a number of "keys turned", it might be argued that in a disease where there are much greater than normal numbers of chromosome aberrations, that is a much greater chromosome instability, then there will be a much greater probability of many of the keys being turned. This will then result in a greater sensitivity (for cancer production) to radiation, considered to be one of the "key turners". Correspondingly, however, one would expect a greater sensitivity to other carcinogens. There is no data on this except in so far that it is known that cancer incidence is high. On this basis the relative risk of radiation induced cancer (compared to other, non-radiation carcinogens) would be the same as in the normal population, although the absolute risk will be higher.

It is difficult to estimate numbers involved. From the evidence quoted, one may be dealing with some thousands of people in a total population of some hundreds of millions, i.e., some thousandths of one percent. It is also noted that survival past childhood would appear to be uncertain without continuing medical care. However, it may be argued that there may be other disorders where the chromosomal instability is less, that persons with such problems may survive reasonably well, and that therefore there may be a larger number with less radiation sensitivity than AT patients but greater than normal.

F.3 Chromosome Aberrations vs. Dose

On the basis that the probability of radiation induced chromosome aberrations may be related to the probability of radiation induced cancer, studies have been made by a number of authors. Such studies have the additional advantage that such aberrations can be observed down to very low doses and so dose-response curves followed to low doses.

A paper by Pohl-Ruling, Fischer and Pohl (Po78) brings together many data on incidence of chromosome breaks as a formation of estimated dose due to both external gamma radiation and internal alpha sources. The alpha data includes persons living in Bad gastein (Austria) where the radon levels are continuously elevated. In the actual spa itself in Bad gastein, the Thermal Gallery has a mean radon level of 3000 pCi/litre air. Other data is from Brazil, USA, Australia, UK, Denmark and Czechoslovakia. The dose-effect curve is distinctly non-linear. The explanation offered by the authors is that at low doses chromsomal damage is mitigated by a constant stock of enzymes - but that at doses around 200 or 300 mrads (per year - the chromosome damage is considered to be integrated over this time), greater production of enzyme is stimulated, so that further damage is eliminated, while above 10 rads the defence mechanisms become overwhelmed.

A conclusion is that extrapolation from high dose rates would underestimate low dose effects and correspondingly extrapolation from low dose effects to effects at 1 rad or greater would greatly overestimate effects.

A point of interest is that the data points for high and low LET radiation are not greatly (if at all) separated. A further point is that errors of orders of magnitude in dose estimation for the alpha emitters would not affect the general shape of the curve.

Chromosome aberrations in exposed workers have also been considered by a group in Colorado (Br78). They looked at both uranium miners and plutonium workers. According to the paper previously quoted (Po 78), their average results agree with those of other workers in this field. In more detail, they found a rising incidence of aberrations with WLM (or in body burden) but also found an apparent decrease in the effect per WLM with increasing dose (i.e., effect would appear to increase sub-linearly with dose).

A study has been conducted in a part of Kerala, India, where the background is 1500 to 3000 MR per year due to monazite sand (Ko76). compared with a socio-economically equivalent area in a nearby but monazite-free region, the frequency of Down's Syndrome and other severe mental retardations of genetic origin was increased (roughly 12:1), while severe mental retardation rates of peri- or post-natal origin were equal in the two groups. Cytogenic studies indicated that although chromatid aberrations were not different in the two groups ($p>0.05$), chromosome aberrations were different ($p<0.01$), with the exposed group having the higher number. Of the 12 cases of Down's Syndrome found (in a population of 12,918) in 11 the maternal age was >30 years, and six of the cases successfully karyotyped had trisomy 21. It is perhaps of interest that the noted frequency of this syndrome in the Neendakara area of Kerala (1:1076) is much higher than that in many parts of the world, as quoted in Ko76; for instance London UK 1:3000, Denmark 1:4000, Australia 1:2083; however, as the authors point out, the Shetland Isles to the north of the UK mainland has a frequency of 1:714.

Data has also been obtained from the monazite Sands areas of Brazil (Ba 75a), where doses inside houses range up to 600 mr/yr. Again, compared with a similar socioeconomic group, there is a significant correlation between total number of chromosome breaks and place of residence ($p<0.05$). Particularly there are more dicentrics and rings, which lead the authors to suggest that the aberrations are due to high LET radiation (internal doses) rather than to low LET external radiation. Although whole body tests were attempted, they were done at such a distance from the place of residence that short-lived daughters had decayed. However, a positive correlations is found between levels of airborne ^{212}Pb and ^{212}Bi in a monazite ore mill and the number of two-hit type aberrations found in the mill workers (Ri75).

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APPENDIX G

CANADIAN AIR STANDARDS

At the time of the concerns in Port Hope about radon and radium levels in the area due to dumping of radioactive material, standards were developed for the area to serve as a guideline for remedial action. In this development, measurements were done of radon levels in homes in a town in the same general geographical and geological area as Port Hope; reasonably, it was felt that natural (i.e. not technologically enhanced) levels in the two towns would be similar. As expected, measurements in the reference town showed a wide variation, with a log normal distribution. A mean and "range" was determined, the latter on the basis of three (log) standard deviations. The upper limit of this "range" was 7 pCi/l of radon; on the assumption that (due to ventilation) radon daughters would have an equilibrium level one third of that of the parent radon, the "upper limit of normal for Port Hope" was taken as 0.02 WL (AECB77).

Such a "natural level" must be peculiar to a particular locality, as natural radioactivity varies widely. It will inevitably be higher on the Canadian Shield than off it. Nevertheless, this level of 0.02 WL has been applied to new building in towns such as Elliot Lake to which people have moved as a direct consequence of uranium mining, though not (in principle) to other places. However the Elliot Lake Environmental Assessment Report of May 1979 also makes reference (Table 12.1) to a figure of 1 pCi/l of radon, 10% of the ICRP radiation worker $(MPC)_{air}$. In the context of this table, this would appear to be a criterion for the open air (radon daughters are stated to be in 100% equilibrium) while the 0.02 WL limit is for inside houses (EAB79).

More recently (McG80), the 0.02 WL figure has been used as a dividing line in the AECB cross-Canada survey of houses, the data being presented in the form of the percentage of houses in a city which have a radon daughter level greater than 0.02 WL. The rationale for this, apart from convenience, is not clear.

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APPENDIX H

GUIDELINES FOR CANADIAN DRINKING WATER QUALITY

For radioactivity in drinking water, Canadian standards and guidelines have been derived from ICRP-recommended limits for occupational exposure. In 1968 (DNHW68) three different levels were delineated for treated or raw drinking water - maximum permissible limit, acceptable limit and objective. These were respectively the ICRP maximum permissible concentration for water for a 168-hour week (ICRP59) one third of that value, and one tenth of that value. This ICRP MPC could result in a person building-up activity such that they would be receiving [illegible] rem in a year (or building up, for instance, 0.1 μCi of radium-226, the MP body burden of this isotope). Alternatively the "objective" could be regarded as being met if the gross radioactivity were [illegible] per litre. [illegible] $(MPC)_w$ (168) as 10^{-7} μC/cc, or 10^2 pCi/litre (3.7 Bq/L), and therefore the "acceptable limit" and "objective" [illegible] and 10 pCi/l of radium. (It is of interest to note that in natural well water tested in a series of measurements around Toronto (Mo61) radium contents tended to be <1pCi/litre while radon activities were well in excess of 10 pCi/litre).

In 1978 Health and Welfare Canada brought out 'Guidelines for Canadian Drinking Water Quality 1978'. These contained "maximum acceptable concentrations" in drinking water of 1% of the "ICRP recommended annual occupational dose equivalent limit for continuous exposure" (i.e., the 168 hr/week), and "target concentrations" which corresponded to 0.1% of those [illegible]. The "Guidelines" gives a maximum acceptable concentration for radium of 1 Bq/litre (based on an annual limit on intake [illegible] of $7 \cdot 10^4$ Bq and two litres of water intake per day, giving [illegible] (27 pCi/ℓ) as the "(MPC)"$_w$) and a target of 0.1 Bq/L - in the older nomenclature, these figures for maximum acceptable and target are approximately 30 and 3 pCi/litre respectively.

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APPENDIX I

CRITIQUE OF EPIDEMIOLOGICAL STUDIES OF ALPHA RADIATION

Introduction

This appendix provides more details on the epidemiological studies described in Chapter 5 and is organized in two sections. Section I.1 describes the studies actually used for risk estimation; additional discussion of the data themselves and any adjustments made to express them in comparable form is contained in Appendix K. Section I.2 describes various other studies not used for risk estimation, either because of inadequate data on risk or on exposure or because of serious methodological problems.

I.1 STUDIES USED FOR RISK ESTIMATION

I.1.1 Czechoslovakian uranium miners.

This is a cohort of uranium miners hired between 1 January 1948 and 31 December 1957 who were exposed to moderately high levels of radon daughters (mean cumulative exposure about 300 WLM). Most of the results are restricted to a subgroup who had started work by 1952 and thus are older and received longer follow-up. The size of this subgroup is not given but can be estimated from the person-years and average duration of follow-up to be about 2200. Lung cancers occurring before the closing dates of 31 December 1973 (Se76, Ku78) or 31 December 1975 (Ku79) were ascertained by registration of cases in health facilities by the study, by the uranium industry, and by a national cancer registry; no information on the completeness of ascertainment is provided. Cumulative radon daughter exposure indices were calculated from work histories and a set of over 120,000 measurements of radon gas levels dating back to the start of follow-up. Measurements of radon daughter/radon levels were made after 1960, and these used to estimate WL at all times. Fewer than 2% of the workers had exposure to any other hard rock mining.

Most analyses are based on life-table comparisons with national male death rates, in which subjects were allocated to cumulative exposure categories based on their final value, and contribute person-years at risk to that category for the entire time since entry. This method will tend to overestimate rates in the lowest category and underestimate them in the highest (En73). The authors recognize this problem in a Letter to the Editor (Ku78) in which they provide a comparison with the "modified life table" technique used by all the other studies. However, in this reanalysis "wasted doses" (those accumulated during the latent period) were included in the exposure index, and this can be expected to have the opposite effect (see Appendix M). For their discussions of modifying factors (Se76, Ku79), the authors use only the "original method", so these results must also be interpreted cautiously. Finally, no account seems to have been taken of the effect of deaths from other causes, though these might be relatively few and independent of exposure.

For the entire cohort, a lung cancer rate of 3720 per 10^6 PY was observed, compared with 750 per 10^6 PY expected. After applying the adjustments described in Section K.2.1, we arrive at an average attributable risk index of 16.82 per 10^6 PY-WLM and an excess relative risk index of 1.92 per 10^2 WLM (Table 5.1). These adjustments are based on an assumption that no excess would have occurred in the first ten years of employment, but still do not eliminate the effect of the wasted doses. Using the original method, there appears to be a slight reduction in slope with increasing dose (Figure 5.2) but comparing the risk index below 200 WLM with that above 200 WLM gives a factor of only 2.32/1.87 = 1.24 (Table 5.2), and the change in slope (if any) does not continue into the lowest group, despite the expected tendency of the method to overestimate risks at low doses. No reduction in slope with increasing dose is apparent using the modified method, but this may be due to the failure to take latency into account.

In summary, the principal strengths of this study are the quantity of exposure data available (though the measurements are of radon gas rather than of its daughters), the number of workers exposed to moderately low doses, and the relatively long period of follow-up (mean 26 years). Its main limitation is the inappropriateness of the methods of statistical analysis.

I.1.2 Colorado plateau uranium miners.

This is a cohort study of 3356 white and 780 non-white uranium miners and millers in the Colorado Plateau who had worked for at least one month underground before January 1964 and had been examined by the Public Health Service between 1950 and 1960. These have been followed from their date of first examination until the close of follow-up, which in the most recent reports (Ar76, Ar78a, Ar80) is 30 September 1974. Though the average period of follow-up is only about ten years, the time since first exposure is of course much longer. The trace rate is greater than 99%, with losses unrelated to exposure. Exposure information was calculated from occupational histories and environmental measurements or estimates. Radon daughter measurements have been made since 1951 but a very large proportion of mine/year combinations had to be estimated from other years or other mines. The amount of error in these assessments has been studied in various ways, and the investigators claim its effect is likely to be slight. In general these miners have been exposed to very high levels of radiation (mean 1180 WLM). Radiation exposure in other hard rock mines has been estimated and included in the individuals' assessments. Results are reported separately in broad categories of the amount of time spent in other hard rock mines; exposure to non-uranium hard rock mining does not appear to have had a substantial confounding effect, but it does reduce the slope of the dose-response relationship, suggesting that its inclusion is adding some random noise to the individuals' assessment.

These data have been extensively analyzed with regard to many factors (Lu71), most results being based on a modified life-table in which subjects are advanced through exposure categories in the correct fashion, except that again, wasted doses have been included in the exposure index. Comparison is with age- and cause-specific death rates for white and non-white males in the four states which contain the Colorado Plateau and results are reported as observed and expected deaths by WLM category and by breakdowns of other variables. To allow for latency, a second set of exposure indices (WLME), based on an accumulation of past exposures with a log-normal latent period, is used (see Sections K.2.2, L.2.1 and M.5 for details). In addition to the factors mentioned earlier, smoking, rural/urban residence, and a general susceptibility specific to underground uranium miners are considered as possible confounders.

For the entire cohort, 159 lung cancer deaths have been observed 10 or more years after first exposure, compared with 25.24 expected, leading to an average attributable risk rate of 3.52 per 10^6 PY-WLM or an excess relative risk rate of 0.45 per 10^2 WLM (Table 5.1). Of all the mining populations described, these estimates are by far the lowest. Excesses are apparent in all categories beyond 120 WLM, but the slope decreases strongly with increasing dose (Figure 5.2), ranging from RRI = 0.92 under 600 WLM to 0.39 over 600 WLM, a ratio of 2.4 (Table 5.2). However like the Czechoslovakia data, this change in slope does not continue into the lowest exposure category.

In summary, this is a large, well traced, and well analyzed study of a group of miners exposed to high levels of radiation. It is also the only study in which data on smoking is available. Its principle limitations appear to be the quality of the exposure data and the small numbers exposed to low levels.

I.1.3 Ontario uranium miners.

In a cohort of about 10,000 miners who had worked in the Ontario uranium mines between 1955 and 1974, 81 fatal lung cancers occurring before the end of 1974 were ascertained (Ha76). No information about the completeness of ascertainment is provided, but there is a noticeable shortfall of deaths from other causes, surprisingly even such causes as respiratory disease commonly found in excess among miners; tracing of this cohort is continuing using a record linkage system at the death certificate registry of Statistics Canada and preliminary indications are that lung cancer had been underascertained by at least 50% (J. Muller, personal communication 1980). For the entire cohort, 45.1 lung cancer deaths would have been expected on the basis of Ontario rates over the entire period. Nineteen of the observed deaths occurred within ten years of first employment, so we have subtracted these from both observed and expected figures for comparability with the other studies (see Appendix K for details). This leads to an attributable risk of 9.59 per 10^6 PY-WLM or an excess relative risk of 3.97 per 10^2 WLM (Table 5.1).

Dose-response information is based not on the entire cohort but on the 81 lung cancer cases and 81 controls sampled from the survivors (He76). These were not matched in the selection process, but subsequently were randomly paired with cases to obtain a comparable distribution of periods "at risk". Cumulative radon daughter exposures were then accumulated for both cases and their paired controls up to the year before the death of the case (again including wasted doses), based on their work histories and environmental assessments (mine averages up to 1968 and personal records thereafter). The distribution of exposures in the controls can then be used to estimate expected deaths by exposure category, as described in Appendix K. Formal justification for the basic sampling procedure and the subsequent analysis has been provided (Li77 and Pr78).

The results show a clear excess in risk beyond 60 WLM with a suggestion of concavity (Table 5.2). The curvilinearity may, however, be an artifact of either shorter latency or better ascertainment (because of compensation claims) at higher doses.

The greatest merit of this study is the very large numbers of men exposed for short periods to low doses (mean 36 WLM). As time progresses, this will become an increasingly important source of data on the adequacy of present standards. The basic case-control strategy is efficient and valid, though a more appropriate selection of controls (Li77) would have allowed better control of age and period-at-risk effects. As it stands, its principal limitations are the very short period of follow-up, the probable underascertainment, the quality of the exposure information, and the failure to take age, year, smoking, other exposures, or any other confounders into account. It is hoped that many of these problems will be overcome as the follow-up study now underway continues.

I.1.4 Newfoundland fluorspar miners.

Preliminary findings have been reported from a cohort study of 2414 males who ever worked for a month or more in any capacity for the fluorspar (calcium fluoride) mines of Newfoundland between 1933 and 1971. Fluorspar is not itself radioactive nor is the rock in which it was mined, but radon gas entered the mines dissolved in under-ground water flowing through them, producing fairly high working levels (mean cumulative exposure 204 WLM). The only published reports (dV64, dV66, dV71, Wr77) describe mortality in the cohort through 1968 in comparison with another town in the same area (Grand Bank) and with the entire province. More recently an unpublished manuscript (dV80) and additional material cited in BEIR80 describe mortality through the end of 1971, for an average of 20 years of observation per person. Seventy-one lung cancer deaths were observed, 65 of them among underground miners. No information about the completeness of ascertainment is provided but it is said to be good (D.T.Wigle, personal communication 1981). Losses to follow-up are treated as alive at the end of follow-up, which would cause excess risks to be underestimated overall and could bias dose-response relations if losses were related to exposure. Exposure indices were calculated from work histories and estimates of radon daughter concentrations: before 1959, on guesses based on the type of job; from 1960 to 1967, on average measured levels; and from 1968 to 1971, on individual-specific measurements. These were accumulated up to each year at risk, with no account taken of latency.

The analysis was carried out by the modified life table method in which subjects moved through accumulating exposure categories (as in the Colorado study). Two standardizing populations have been used. For a description of mortality in the entire cohort, Newfoundland rates were applied to the cohort after excluding the first ten years after start to produce an estimate of 3.76 expected lung cancer deaths (BEIR80). In this subgroup, the cumulative exposure was 248 WLM, leading to an attributable risk of 17.82 per 10^6 PY-WLM (Table 5.1) or an excess relative risk of 6.57 per 10^2 WLM. However, the Newfoundland rates almost certainly produced an underestimate of expected incidence, as smoking was said to be exceptionally common amongst the miners. Hence, in other analyses, the rates in the complete cohort were used as the standard, and the expected deaths were scaled so that expected equalled observed among the surface workers (see Appendix K); for these analyses, man-years in the first ten years of employment are included. On this basis, 9.69 lung cancer deaths among underground workers (mean exposure 204 WLM) were expected, against 65 observed, giving a relative risk of 2.30 per 10^2 WLM (Table 5.1).

Detailed dose-response information is available only for the latter analysis. It suggests some concavity (RRI = 1.73 per 10^2 WLM for 1-479 WLM or 2.83 for 480+ WLM, Table 5.2). However, these findings must be considered fairly cautiously because of the three biases discussed in Section 4.2.1.1: first, none of the standardizing populations provide a reliable basis for computing expectations, and arbitrarily pegging internal comparisons to the six observed deaths among surface workers is quite tenuous; second, errors of measurement of exposure are probably substantial; and finally, no account is taken of latency, either by excluding early years at risk or through accumulating exposures to some interval before death.

In summary, these data have several important limitations, notably the quality of the exposure data, the lack of a suitable basis for estimating expected deaths, and the failure to take latency into account. Information on smoking and on the trace rate would also be desirable, but this is also true of most of the other studies.

I.1.5 Swedish metal miners.

Mortality has been described in three mining areas of Sweden (Table 5.1), Kiruna (Jo73), Zinkgruven (Ax78), and Malmberget (Re74) but none of these provide detailed dose-response information (see section I.2.4 for a description of these studies). However, one preliminary report of a national survey (Sn73) provides a breakdown of risks by exposure category. While their methods of environmental measurement and control are described in detail, very little is said about their epidemiologic methods. Overall, thirty-six lung cancers have been observed compared with 6.07 expected, producing an attributable risk of 3.43 per 10^6 PY-WLM or an excess relative risk of 3.03 per 10^2 WLM. One table is provided giving a comparison of mortality rates in four overlapping exposure categories. These show a considerable decrease in slope with increasing exposure (RRI = 4.24 per 10^2 WLM in the two lowest groups vs 2.82 in the two highest). However, as the groups overlap in exposure, it is likely that these groups may represent entire mines rather than individuals, and thus the comparison may be subject to confounding.

I.1.6 Atomic bomb survivors.

By far the largest population for study of the effects of moderately low doses of radiation is the cohort of 82,000 survivors of the atomic bombs at Hiroshima and Nagasaki. An additional 27,000, who were not in the city (NIC) at the time of bombing but who entered soon after, have been described (Hi68, Be71), but are not included in the results described here.

The most recent and comprehensive report (Be78a) describes mortality over the period from 1950 to 1974. The Japanese family registration system was used to ascertain the fact of death, and cause of death was obtained from death certificates by special arrangement with the Ministry of Health and Welfare. Thus losses to follow-up are virtually nonexistent (about 0.1%) but ascertainment of specific causes varies depending on their diagnostic accuracy. For lung cancer, the specificity of the certified cause of death has been estimated at 85% and its sensitivity at 45%, based on an autopsy series (St76). Tumor registries have also been established in each city and are probably less subject to diagnostic error than the death certificates, though ascertainment is believed to be less complete at Hiroshima than at Nagasaki. The accuracy of either source of data could be related to radiation dose, but these data have not been critically examined (BEIR80).

Radiation has been estimated on the basis of the subjects' distances from the hypocenter, with some adjustment for shielding (No76, Au75, Ha75). These estimates are provided in the form of tissue kerma in air doses ("T65", in rads) from gamma and neutron radiation, and subjects are grouped according to categories of the total of these two components (i.e. assuming an RBE of 1). An important feature of these data is that the two bombs differed in the relative importance of the two components. We have taken two approaches to this problem. First, using estimates of the ratios of absorbed to kerma doses (Ke79, as quoted in BEIR80, Table V-6) and an assumed quality factor for neutrons of 10, we have estimated a mean dose equivalent (in rems) in each of the T65 dose groups (see Appendix K for details). Second, we have used a weighted least squares fitting procedure to estimate a separate slope and exponent for each radiation component, though we have subsequently abandoned this approach because of the recently released discovery of errors in the assessment of these two components of exposure (Lo80).

The analysis of mortality involved cross tabulating the deaths from each cause and the person-years at risk by age, sex, year, city and kerma dose. City- and dose-specific expected deaths are then estimated by standardizing across age, sex and year categories using the Mantel-Haenzel method (Ma59). The comparison is thus against the total cohort rather than against national rates, so where there is a radiation effect, observed deaths will be less than expected in the lowest exposure groups. We have also taken two approaches to determining intercept. First, we have multiplied all expectations by a constant factor for each city to set the observed equal to expected in the zero-dose group. Results are then reported only for the higher dose groups. For Hiroshima, this provides quite a good intercept as there are many lung cancer deaths (105) in the zero-dose group; for Nagasaki there are only 16, so the remaining expectations become quite imprecise. Secondly, we applied weighted least squares to all dose groups to estimate the intercepts in each city as additional free parameters.

Using the zero-dose group as the reference, 152 lung cancers were observed at Hiroshima compared with 109.50 expected and 57 observed at Nagasaki compared with 46.46 expected. Using the dose equivalent described above (assuming Q=10), these lead to estimates of attributable risk of 1.74 and 0.84 per 10^6 PY-rem respectively and of excess relative risk of 1.02 and 0.56 per 10^2 rem respectively. Using the dose equivalent, there is a measurable dose-relation of both cities, though it is apparent in Nagasaki only after regrouping to three categories (0, 1-99, 100+ rad kerma), and the slope there is only about half that at Hiroshima. The Hiroshima data show greater convexity than any other study (RRI = 1.96 per 10^2 rem for 1-99 rads kerma, versus 0.45 for 100+ rads, Table 5.2). The Nagasaki data are too few for reliable inferences on curvature, but suggest slight concavity.

Except for the purpose of providing an upper limit to curvilinearity, we have not included the atom bomb survivors with the five mining populations in the synthesis described in Section 5.1.2 for several reasons. (1) The exposure is for a combination of gamma rays and neutrons rather than alpha particles; as we have seen, there appears to be essentially no prospect for separating the two effects and even if there were, a further assumption would be needed to justify combining neutron and alpha particle data. (2) It has been suggested that the survivors of the blast represent a fitter subset of the population who might be less susceptible to the carcinogenic effects of radiation. For example, the leukemia risk among early entrants ot Hiroshima is larger than that among those blast survivors thought to have received similar doses (Ro77). It is possible (though perhaps somewhat improbable) that such a selection bias could increase with increasing dose, thus explaining the convexity. There is less reason to expect such a "survival of the fittest" effect among miners. (3) The accuracy of lung cancer certification is very poor, and the diagnostic errors may be dose-related (though this is less likely than for the well known radiogenic sites like leukemia). (4) There may be important social or racial differences in susceptibility to lung cancer; Japanese residents do have a lower natural incidence at this site which is less than one-third that of North Americans (Se69). (5) Finally, the Oak Ridge dosimetry group has discovered some problems with the T65 dosimetry calculations which affect the neutron component more than the gamma (Lo80).

In summary, the principal merits of these data are their very large size, particularly at low doses, and the completeness of tracing. Its limitations are the accuracy of diagnosis for lung cancer and other causes, the difficulty of unscrambling neutron and gamma effects, and the possibility of a natural selection effect.

I.1.7 Female radium dial painters.

This is a cohort study of females employed in the United States radium dial-painting industry before 1930, followed to 1976 (Ro78a). They had ingested ^{226}Ra and ^{228}Ra isotopes, which are bone-seeking radionuclides, through the practice of licking the paint brushes to get a fine point. Out of the 1474 women ever employed in the industry before 1930, a cohort was defined, consisting of the 759 women whose radium body burden had been determined. They were identified in various ways and may well not be representative of the total population at risk. The cohort was followed from first exposure until the end of 1976, an average period of follow-up of about 50 years, making this the longest cohort study of alpha radiation available. However, ascertainment may be biased in a number of ways: the earliest cases to die may be under-represented and some of these may have died from high doses of radium; on the other hand, those who ultimately suffered from the effects of radium may be over-represented--for example, of those known to be deceased, the proportion of bone sarcomas in the measured cohort is roughly double that in those not measured; finally, some of the unstudied deceased cases have been exhumed but as this program has been only partially complete, biases may have been introduced. Exposure was assessed in two ways, by systemic intake (a measure of ingested activity in microcuries, estimated by extrapolation from measurements of body content at later times) and average skeletal dose (a measure of cumulative exposure up to some interval before death, in units of rads). These calculations require an assumption about the effectiveness of ^{228}Ra relative to ^{226}Ra, and a value of 2.5 (an average of estimates by three different methods) has been used. Two endpoints are of particular interest: in the 759 measured cases there have been 38 bone sarcomas and 17 carcinomas of the mastoid air cells or paranasal sinuses ("head carcinomas").

As both are extremely rare in the general population it is reasonable to assume that all of these cancers were attributable to radiation. Hence the analysis consists of fitting the cumulative incidence rates to measures of dose, where the latter are invariant over time. The measure of cumulative incidence rate used is number of cases divided by person-years at risk starting five (for the sarcomas) or ten (for the head carcinomas) years after first exposure. These rates (not age-adjusted) are then fitted to the usual linear-quadratic-exponential function used in radiobiology using a weighted least-squares procedure. Both cancers were found to be strongly exposure related, and a quadratic-exponential relation fit well to the sarcoma cases while a linear function fit well to the head carcinoma cases, other models being rejected. The principal strengths of this study are its very long period of observation and the fact that the cancers studied are probably all radiation induced so that confounding factors can be largely ignored. Its limitations are that only about half (probably a biased subset) of those exposed were measured, and that there is some doubt about the accuracy of the dose measurements.

I.1.8 Radium injections.

This is a cohort study of German patients injected with ^{224}Ra for treatment of bone tuberculosis, ankylosing spondylitis and other disease mainly during the years 1944 to 1951 (Sp70, Sp78, Ma78). The total of 977 were then followed until 1969. The patients were identified through hospital and doctors' records rather than as a result of the appearance of disease. No information is available on the completeness of case ascertainment. The exposure was estimated in terms of average skeletal dose in rads from information about applied doses contained in the medical records. Soft tissue tumors and blood dyscrasias were analyzed but not found to be related to radiation. The 49 bone sarcomas were found to be strongly dose-related, but a variety of dose-response models provided an adequate fit to the data. There appeared to be a suggestion of a negative relationship of latent periods against dose. As with the radium dial painters, a strength of this study is that the sarcomas were probably all radiation induced. Information on dose is better than in the other study. The period of follow-up is much shorter, but ascertainment is more complete.

1.1.9 Thorotrast.

Thorotrast, a colloidal suspension of thorium dioxide in dextrin, was first used for radiography in man in the late 1920's. In many ways it is an ideal radiographic contrast medium, being non-toxic (chemically) and non-corrosive, stable, and having a very high atomic weight (and therefore being very radio-opaque).

Frik, Head of the Institute of Roentgen Research in Berlin, used thorotrast for animal experiments. Radt in the same hospital used thorotrast for visualizing the liver and spleen of rabbits, and started using thorotrast in man for hepatrography. At the same time work started in Japan (Ca67).

The question of possible radiation damage was discussed but it was concluded that no risk existed, on the basis of two years experience with animals and of shorter term (e.g. 5 months) studies in humans. The US literature on the effects of alpha radiation on humans (e.g. the radium dial painters (Ma25)) was not read in Berlin, and so possible effects from thorium were not realized.

The radiographic value of thorotrast was such that it was used for a variety of clinical purposes for many years - in Portugal, for instance, until 1955. Most of the examinations in Portugal were for cerebral angiography, and in 3/4 of all cases the thorotrast was injected systemically into the blood stream. A total of over 2000 persons in Portugal seem to have had a thorotrast procedure, while in Germany the records of 50 West German hospitals showed more than 5000 cases who had thorotrast intravascularly.

In another type of procedure, performed in North America, thorotrast was used to visualize the spina column. This myelography was carried out about 1940. Again the procedure was used because of the excellent radiographic contrast obtainable and because thorotrast gave less local irritation than did other possible contrast media. It was appreciated that radioactivity problems might exist, and to mitigate these, attempts were made, after the radiography, to remove the thorotrast that had been pumped into the spinal fluid. Such attempts were rarely better than 90% efficient, and commonly much more was left in the spinal column, where it often puddled down to the lower spine, the region of the cauda equina, where many of the nerves for the lower part of the body leave the spinal column.

In a study carried out in West Germany (vK78), 5159 cases involving thorotrast were considered. An equal number of pseudo-randomly selected controls were taken from the same hospitals as the thorotrast patients, the controls being age and sex-matched. Of the 5159 patients, 1918 died from their primary disease within 3 years of the thorotrast procedure and were excluded from the study. Of the 1257 who had died more than 3 years after the procedure but before the investigation began (i.e. 3 < t < 25 years), the mean survival time was 18 years; 311 died of diseases (such as cancer) which could reasonably be associated with uptake of the thorotrast while the control group of 1168 persons had only 86 deaths of the same nature - the relative risks (cases among the exposed divided by cases among the unexposed) of liver tumours were 107/5, myeloid leukemia 17/2, cirrhosis of the liver 126/37. On the other hand, lung tumours (included in the above totals) were 29/28, and lymphatic leukemia 2/2.

Of the 851 patients alive at the beginning of the study and examined clinically, 155 had developed or did subsequently develop "diseases of interest", as against 6 out of 647 controls. The relative risk of liver tumors was 75/0, of myeloid leukemia 5/0, of cirrhosis of the liver 56/3 and lung tumour 8/3.

There was a latency period in all cases (though any deaths within 3 years were excluded). Leukemia started to occur 5 years after thorotrast injection and showed a continuing increase with time (mean 19.5 years). Liver tumours were not observed until about 20 years after injection and thereafter their number increased very rapidly (mean 27 years).

Although the amount of thorotrast injected is known rather well, it is difficult to estimate the radiation dose accurately in any tissue. Part of the reason is the normal problem of metabolic distribution and redistribution of the material in the body, but there is the additional complication that the thorotrast is in aggregates, and there may be considerable self-absorption of alpha ray energy in the aggregates. For the standard dose of about 25 ml, an estimate of dose rate to the liver is 25 rads per year (vk78) but the width of variation might be 10-50 rads in individual cases. Taking 20 years as the average induction period for liver tumors, the average effective dose to the liver is 500 rads. For cirrhosis, the mean latent periods were somewhat shorter (23 years) but the dose accumulated during the entire period is probably relevant, so we will take the same estimate of total dose. For leukemia, the estimated dose rate to the bone marrow is 9 rads/year, which multiplied by an assumed average induction period of 10 years yields a cumulative estimate of 90 rads.

The same calculation gives a dose rate of 1-5 rads/yr in the bronchial region. Over 30 or so years 30-150 rads or 600-3000 rems would be received. Taking for discussion purposes a relationship between dose equivalent to the bronchial-region and WLM of 8 rem = 1 WLM (Appendix E.1.5), then figures suggest the equivalent of 80-400 WLM. This is in the range in which positive relationships are seen in miners between lung cancer and occupational exposure to radon daughters. In a population of 2000 with a mean exposure to 250 WLM (for the sake of argument), the Czechoslovak mining data would predict 120 extra lung cancers (or a relative risk, observed/expected, of 5 times). This is not seen in the thorotrast patients. As noted before, in the deceased patients the ratio was unity (29/28) while in the patients alive at the beginning of the study, the ratio was 8/3 (which is indeed consistent with almost any ratio between 1 and 5). It should be noted that the average age of the patients deceased-prior-to-investigation was 40 at time of thorotrast procedure, while that of the alive-prior-to-investigation group was 20 - this may partially account for the apparent discrepancy. Different latency periods for different diseases may account for the differences between the thorotrast data and the Czech data; the liver cancers may have caused death before lung cancer became apparent as the mean survival time of the patients was 18 years.

The Portuguese study (Ho67 and Ma67) consists of 2,382 persons injected with thorotrast for radiological reasons between 1930 and 1955. Of these, 1871 had the injections into the blood stream, with about 25 ml again being an average dose . Between 1961 and 1966 about 50% of the patients had been traced, and 387 of these were still alive. In the 1120 persons traced, there were 76 diagnoses of fibrosis or hemangioendotheliomata of the liver (47 and 29 respectively), nine myeloid leukemias and 31 other malignancies. Of the 733 deaths in this group, 101 could reasonably be ascribed to thorotrast "side-effects". This is a rather smaller percentage (15%) than in the German study (25%) noted above, although the doses were similar. Carcinoma of the bronchus was diagnosed in 5 cases. This is only 0.5% of the 921 deceased patients who had been systemically injected with thorotrast during the period of 1930-1949 and followed to 1963, but compared to the expected death rate at that time for the Portuguese population (0.96 expected), the number is stated to be highly significant (p = .003). The 5 deaths from lung cancer in 921 is still nowhere near the 100 or so expected on the Czech data, following the arguments given above and making the reasonable assumption that the radiation dose rates would be similar to those calculated for West Germany (as the thorotrast dose given was similar).

With respect to effects of thorotrast myelography, published numbers are smaller but effects equally dramatic. In one hospital in Canada, 27 patients were given this procedure (McN68). Of 15 patients traced, 12 had progressive dysfunction of the cauda equina or serious cauda equina deficit.

Measurements of thorium burden were carried out on those traced and alive; on the basis of subsequent animal experiments calculations were made of the dose received by the patients. The dose to the cauda equina accumulated to onset of myelopathy was in the range 2 to 28 kilorads. It is of interest that (excluding one man whose time of onset of myelopathy, 2 months, was so short that radiation was almost certainly not the cause), the onset of myelopathy occurred rather tightly around 16 years after thorotrat procedure, independent of the estimated total dose (and therefore independent of dose rate).

I.2 STUDIES NOT USED FOR RISK ESTIMATION

I.2.1 South African gold miners.

Mortality has been described in white males working in South African gold mines (Ba72), where uranium is always present in small quantities, producing radon daughter concentrations below 1 WL (Gr70). This is essentially an historical cohort study, in which cases were ascertained from the Miner's Medical Bureau (by way of the Pneumoconiosis Research Unit, PRU) and the population at risk was estimated by a random sample of those registered with the Provident Fund (PF). The numerators consisted of all lung cancers known to the PRU between 1949 and 1967. These were certainly underascertained, particularly in the early years; ascertainment has been estimated elsewhere to be about 80% since 1960. Only cases for whom employment records could be found and who had been underground gold miners were used. The denominators consisted of a random sample of 1100 out of 227,000 subjects listed with the PF before 1967. Only those whose work histories could be found, who had worked underground in gold mines, and who were still alive in 1967 were used. The exclusion of 99 deaths before 1967 and 17 losses means denominators were also somewhat underestimated. Cumulative shifts worked and WLM's were estimated for both numerators and denominators year by year from work histories and radon daughter measurements, which were however available in only 12 out of 119 mines. As WL estimates were distributed over a fairly narrow range, these two indices were strongly correlated. The analysis consists of crude rates reported by year, age, cumulative shifts, and WLM separately. No attempt was made to standardize each effect for the others. The observed death rate for lung cancer was estimated to be $296/10^6$ PY, which was found to be within the range of expected death rates estimated in various ways. Rates were found to vary strongly with age, shifts and WLM's but because of the lack of adjustment, these results are uninterpretable. The fundamental limitations of the study are the uncertainties in the ascertainment of both numerators and denominators (even though the basic sampling scheme is sound) and the failure to provide estimates of risk in terms of WLM adjusted for age.

I.2.2 U.K. Haematite Miners.

A proportional mortality analysis of deaths amongst iron ore miners in the Cumberland district of the U.K. between 1948 and 1967 has been reported (Bo70). A separate survey (Du70) has shown that these mines have had moderately high concentrations of radon daughters (ranging from 0.15 to 3.2 WL). All male deaths over 15 years occurring in the two administrative districts in which most of the miners lived are reported, broken down by age, district, cause of death, and occupation as stated on the death certificate. These may be biased by migration and/or by errors in the occupations given on the death certificate (the "promotion effect" Li60, Li77). The numbers of deaths occurring among underground miners was compared against an expectation based on local non-mining experience and on national rates using the age-adjusted proportional mortality method, excluding other cancers and respiratory disease. Thus the 36 lung cancers in underground haematite miners compare with expectations of 20.58 or 21.48. This form of study is highly susceptible to bias in ascertainment of disease and exposures, and may misrepresent risks if other causes are also affected by exposure (though the obvious risks of mining have been eliminated in the comparison). However its principal limitation is the lack of any individual measurements of exposure. Thus it could contribute at most a single estimate of risk in relation to average concentration (assuming the entire excess were attributable to alpha radiation) and even then it would not allow an estimate in relation to cumulative exposure without making further assumptions about the average duration of exposure.

I.2.3 Swedish Studies

In addition to the national survey (Section I.1.5), three studies of non-uranium miners and one of Swedish residents provide single point estimates of risk, but no breakdowns or risk by exposure categories.

The most informative of these is a case-control study of 29 lung cancer deaths occurring in the parish in which two lead-zinc mines were located (Ax78). The radon daughter concentrations were below 1 WL. For controls, the three persons (presumably males) listed in the death register immediately before and immediately after each of the cases were selected; these thus totalled 174. The mining companies then indicated whether each of the subjects had been exposed underground and whether or not they had been a smoker; no assurances are given that this classification was done blind. Relative risks are reported only for the fact of exposure underground (adjusted for age) and for smoking (among miners only, adjusted for age, length of underground exposure and, apparently, smoking again). An adjusted rate ratio of 17 is found for exposure underground and of 0.5 for smoking. The latter finding (i.e. that smoking appears to decrease risk of lung cancer) leaves one somewhat suspicious about the quality of the smoking data. In any event, the small number of cases, the lack of a quantitative measure of exposure (except for a single overall estimate of 110 WLM quoted by Ax78b but not given in the original paper), and the incorrect analysis of exposure-smoking interactions renders this data of only slight value in the overall picture.

Fourteen lung cancer deaths have been reported among "active" underground miners aged 20 to 64 at the Malmberget iron ore mines (Re74). Based on the death rates for the predominantly rural middle and northern Sweden with mining communities excluded, 1.03 lung cancer deaths were expected. However, as semi-rural or urban rates might have been more appropriate for comparison with a mining community, the total population of Sweden has been used to arrive at a revised estimate of 2.95 expected lung cancer deaths (ar78b). Radon daughter concentrations of 1-2 WL have been found in several areas of the mine, but the origin of the figure of 170 WLM for the mean cumulative exposure (Ar78b) is not stated.

A proportional mortality study in the Kiruna iron ore mining district found 13 lung cancer deaths among underground miners compared with 4.47 expected based on local rates or 4.21 based on Swedish rates (Jo73). These are said to relate to about 1900 men at risk on average for about 15 years and exposed on average to 110 WLM (Ar78b), but again the origins of these figures are not explained.

Finally a case-referent study of lung cancer in rural Sweden in relation to type of dwelling found that residents of stone houses with basements (mean radon concentration 1.9 pCi/l) had a five-fold higher risk than those living in wood houses without basements (mean 0.5 pCi/l), others occupying an intermediate position (Ax79).

I.2.4 Thorium Workers.

Three studies are "now in progress" in a thorium refinery (Ru79): a historical cohort mortality study of all those who ever worked at the refinery and for whom a start date is known (3969 employees, of whom so far 630 are known to be dead); a cross-sectional morbidity study by questionnaire of all males who worked for a year or longer and are still alive (431); and a medical examination of 100 workers randomly selected from the questionnaire survey group. Individual exposure indices will be computed from work histories and a hygiene survey carried out in 1955; it is not stated whether these environmental measures have been brought up to date. So far no results have been reported. Thorium and its daughters emit alpha, beta, and gamma rays and it is not clear which is likely to be the most important component.

I.2.5 Hanford Works.

This is one of the largest nuclear plants in the United States; most of the staff are involved in some way with the manufacture of radioactive substances. The NCRP standard of 5 rem per year has been rigidly enforced since the plant went into full production 1944. This study (Ma77, Kn78, St80) is only peripherally related to alpha radiation, as the Hanford workers were exposed both to penetrating external and to internal radiation, and the only measure of the latter is whether a positive urine analysis was ever reported. (It is not clear whether this analysis was only for alpha radiation or also for, e.g. tritium).

This is basically an historical cohort study, but virtually all analyses are based on a comparison of cancer versus non-cancer deaths, i.e. essentially a proportional mortality analysis. In the discussion, some preliminary comparisons with survivors to 1973 are provided, but these are largely uninterpretable. The cohort consists of 24,939 persons who were employed at the Hanford Works between 1944 and 1971. 38% were "early discharges" (i.e. discharged within the year of hire or the year after), many of whom (e.g. construction workers) would not have been members of the "monitored population". Mortality to the end of 1972 is described, consisting of 3710 deaths, all but 213 of whom had a certified cause of death. Deaths were identified from social security death benefit claims and those not identified were presumed alive in 1973. No information is provided about the completeness of follow-up except that it is better for males than for females; if ascertainment were jointly related to exposure and cause of death, bias in the proportional mortality results could have resulted. Two indices of exposure were used: cumulative film badge readings integrated to each year at risk, and whether urine analyses of internally deposited radio nuclides had ever been positive. However not all subjects were monitored by both methods and no information is given about the completeness of either method of monitoring. It may be reasonable to suppose that those not monitored for external or internal radiation received essentially zero doses, but there seems to be some ambiguity about this.

The main form of analysis is a comparison of mean external exposures in cancer deaths (by site) with that in non-cancer deaths. Except for particular analyses, the period of integration of exposure is up to death, raising the possibility of the bias that those living longer would have the opportunity to accumulate larger doses (En73). The fact that the survivors accumulated the largest exposures is evidence of this effect. Usually, the effect of this bias is to dilute the real effect of exposure, but in a proportional mortality analysis this is not necessarily so: if the cancer deaths occurred at older ages than other deaths, for example, this might explain their higher doses. The authors present some age-adjusted findings to refute this explanation, but the results would have been more convincing if exposures were integrated to comparable times and comparisons properly adjusted for age and other factors. Furthermore, the authors rely on the comparison of mean exposures in cancer and non-cancer deaths as a test of the null hypothesis and as a method of estimating the doubling doses; while this is true if the linear model is correct, the analysis would be much more informative if estimates of risk as a function of dose had been provided.

Keeping these limitations in mind, the data purport to show the following: (a) that among a population supposedly exposed within currently accepted standards, excess risks for cancers of 9 sites can be identified; (b) the estimate of the radiation effect depends on the point in time to which the exposure index is accumulated and the age at exposure; (c) taking latency into account, estimated doubling doses are very much lower than other studies would indicate; (d) however, external radiation accounts for only part of the excess; (e) internal radiation may be a factor in explaining some of this discrepancy (though the thrust of the paper is on explaining the variation with respect to external radiation adjusted for internal, rather than the other way around); and (f) overall, about 6% of the cancer deaths might be attributable to radiation exposure.

The principal limitations for our purposes are the absence of a suitable measure of alpha radiation and the confounding by external radiation. In general the results would be much more informative if presented in terms of risk as a function of dose rather than as mean exposure in cancer and non-cancer deaths. This has been done in a number of recent reanalyses of these data (e.g. Da81, Ma78, Gi79a,b, Go79, An78, Hu79), a review of which would be beyond the scope of this report.

I.2.6 Mortality and radon-daughter concentrations in 13 Canadian cities.

This was a descriptive study examining the correlation between mortality rates and average indoor radiation daughter concentrations in 13 Canadian cities (Le80). The radon daughter measurements were obtained from a study of 10,000 homes selected according to a random sampling scheme established by Statistics Canada. Radon daughter concentrations were generally very low (geometric means in the cities ranging from 0.0009 to 0.0036 WL) and highly skewed (McG80). The percentage of homes in which radon daughter concentrations exceeded 0.02 WL was therefore chosen as the more sensitive and stable index of exposure; this ranged from 0 to 7% in different cities. No evidence of any substantial association between lung cancer or general mortality rates and indoor radon daughter concentrations was found. Given the low exposure levels (which would lead one to expect very low risks) and the impossibility of controlling confounding effects or of relating exposure and disease in individuals, it is hardly surprising that the results of such a study would be negative. A proposal is made for a case-control study in one or more of the highest risk cities, for which individual measures of exposure could be obtained and confounding variables controlled; this proposal appears to be worth pursuing.

I.2.7 Mortality in ship-yard nuclear workers.

This was a proportional mortality analysis of deaths occurring at the Portsmith Naval Shipyard (PNS) where nuclear submarines are repaired and refueled (Na78). Deaths were ascertained by reviewing over 100,000 death certificates from new Hampshire, Maine and Massachusetts between 1959 and 1977, looking for a stated occupation at the Portsmith or Kittery Naval Yards. In this way, 1722 deaths of PNS workers were identified. About one-third of these were investigated to determine whether or not the subject had been involved in nuclear or non-nuclear work. Observed numbers of deaths in each group for various types of cancer were compared with those expected on an age- and year-adjusted proportional basis. These revealed a substantial increase in leukemias and minor increases for other cancers. However no estimates of the exposure to external or internal radiation is available. Furthermore the study is subject to bias both in the ascertainment of cases and the accuracy of the exposure histories. Subsequent investigation by an historical cohort study using exposure records failed to confirm these findings (Ri81).

I.2.8 Mortality in Port Hope.

An examination of cancer death rates in the Port Hope area, 1976 to 1978, is in progress. Preliminary results (OCTRF79) fail to find any substantially higher rates than expected based on age-adjusted Ontario rates. No data on the type or levels of radiation exposure have been reported. The possibility of a controlled cohort or case-control study is under consideration.

I.2.9 Uranium City miners.

This is a small (249 miners plus 123 male controls) cohort study of the initial prevalence and subsequent incidence and progression of precancerous lesions by sputum cytology in the uranium miners of Eldorado Nuclear Ltd., Uranium City, Saskatchewan. Reports to date (Ba78, Ba80) describe only prevalence, so the reported associations with smoking and radon daughter exposure are largely uninterpretable as these effects could be due either to associations with incidence or duration. No results for incidence of frank lung cancer or mortality are yet available, nor are they likely to be very reliable because of the small sample size and short period of follow-up. The study also suffers from various methodological problems and is not well described.

I.2.10 Port Radium miners.

A preliminary report of the mortality experience of Eldorado Nuclear Ltd.'s uranium miners at Port Radium, N.W.T. has recently been published (Gr80). A clear excess of lung cancer (RR = 36, at least among deaths occurring in Alberta) is apparent among those who worked at least five years underground, but no data on exposure levels is provided. Further tracing efforts are planned but it appears that exposure data may never be available.

I.2.11 Studies of background radiation.

Several surveys of mortality in geographic areas with different levels of background radiation have been done, but none provide convincing evidence of a dose-response relationship, particularly when the difficulties of controlling for confounding factors are considered. The main importance of these studies is to provide an upper limit on the possible magnitude of the radiation effect at low levels, since any dose-response model which predicts a cancer effect at the background level greater than the natural rate of cancer is clearly untenable (Co80). While the argument applies to any form of radiation, for high-LET the relevant background level would be presumably be for radon daughters, and here the role of smoking would have to be carefully taken into account.

I.2.12 Welding.

Thorium is added to the extent of 1 or 2% in electrodes used for welding stainless steel. If the electrode touches the weld, it may be burnt and the electrode is reground on a wheel. These operations may result in dispersion of thoron. Grinding dust is found to have a total activity of the order of nanocuries per gram, consistent with the above percentages. The dust particles are expected to be large, of the order of many μm, and will largely be stopped in the nose and pharynx. It would seem unlikely that the activity of airborne dust would be significantly greater than 0.1 pCi/ℓ, the "normal" value.

I.2.13 Thoron from Gas Mantles.

Thorium oxide is used in the production of gas mantles. As a result the air in factories making them has a higher than normal thoron content. "Normal" is around 0.1 pCi/ℓ, whereas the air of mantle factories "has been found to range from 23 to 400 $\times$ 10^{-11} Ci/ℓ of air" (Ev40), that is, 230 to 400 pCi/ℓ or around 30-500 WL (assuming equilibrium with daughters and recalling that for thoron 7.3 pCi/ℓ is 1 WL). In a meso-thorium refinery the "emanation content of the air varies between about 40 to 600 $\times$ 10^{-11} Ci of thoron per liter" (quoting from the above paper) that is, possibly up to 60 to 900 WL. The two sets of values are of the same order as the radon concentrations in air in the Erz mountain mines. However Evans and Goodman (Ev40) quote only one case of injury to a worker in the meso-thorium factory, who showed a blood change which indicated a tendency to leukemia but which returned to normal after leaving the refinery. The worker had "presumably part time work for less than 1 year", i.e. a maximum of 10,000 WLM. This maximum must however be a gross overestimate as it implies an equilibrium between thoron and all its daughters, whereas with any reasonable ventilation the 10 hr ThB will be almost entirely swept out; as remarked in Section E.7, it is this isotope which is the main contributor to WLM (and dose). A reduction by a factor of 40 (10 hr/15 min.) in WL is not unreasonable, and the TB region of the lungs would then get a rad dose 10 or 50 times less per WLM from Tn daughters than from Rn. These two factors may well reduce the effect of the apparent 10,000 WLM to the equivalent of more like 5 to 25 WLM. Under these circumstances, the chance of producing bronchial cancer is small.

I.2.14 The MIT-CHR Radium Series.

In addition to the radium dial painters described above, further populations of radium exposed persons have been assembled at the Massachusetts Institute of Technology (Ev74) and Argonne National Laboratories (Fi69b). The two series were combined around 1970 and all further studies have been carried out by the Center for Human Radiobiology (Ro78b). These comprise a variety of types of exposure, not clearly distinguished in the various reports, including medical patients, dial painters, radium chemists and others. Efforts have been made to exclude from the series those who were ascertained as a result of adverse effects of radium, but no clear definition of a cohort and no description of its completeness of tracing, ascertainment methods, representativeness with respect to exposure, etc. are provided. Keeping these limitations in mind, the data are more consistent with the quadratic-exponential relationship shown for the dial painters than the linear-exponential relationship in the German series; however, the possibility that this apparent threshold behaviour could be due to underascertainment among the less exposed should be considered. Evans (Ev74) has emphasized the inverse relationship between dose and "epidemiologic latent periods" (ELP, Sections 7.2.2 and M2) and, by fitting a power function to these data, has argued for a "practical threshold", that is a level of dose below which the ELP would exceed the lifetime. However, two criticisms of his approach could be made: first, his analysis of ELPs suffers from the failure to take censoring of mortality and protraction of dose into account, which can bias the relationship as discussed in Appendix M; second, the use of a power function loads the dice in favour of his hypothesis since at low doses the curve diverges to infinity--a linear relationship between dose and ELP would probably fit his data as well and, when projected to low doses, would still predict a finite latent period.

A recent report (Ad80) describes an excess incidence and mortality from breast cancer in the cohort of female radium dial painters first employed before 1930. Unfortunately, though a number of variables are described, intake is described only in two categories (above or below 50 μCi) so nothing can be deduced about the shape of the dose-response curve. This excess of breast cancer was not confirmed in another study of dial painters (Po78).

I.2.15 Human plutonium exposures.

Plutonium is an alpha emitter which may be inhaled or ingested as a result of environmental or occupational contamination. In animals (e.g. Ba74), it has been shown that lung and bone are the prime targets of cancer induced by plutonium radiation.

Some human studies have also been carried out on persons working at, or living near, Los Alamos (NM) where plutonium was processed in the Manhattan Project (Vo78). The most contaminated group was of 26 workers, who in 1975 had a range of plutonium burdens from 6 to 230 nCi, as a result of accidents in 1944-45. None of these (now of mean age 56) had contracted either lung or bone cancer. A larger group, consisting of 224 persons who had body burdens in 1974 of more than 10 nCi has also been followed. Compared to US white male rates (race, age and sex matched) the mortality rates are significantly lower (perhaps because of the "healthy worker effect"). For lung cancer, 3.2 deaths were expected and 1 observed; for all cancers, 10.9 were expected and 7 observed.

It is of interest to see if the null results on lung cancers are consistent with the results found with inhaled radon daughters. Cohen (Co77) has used ICRP lung models to calculate dose equivalent to lung tissue from inhaled ^{239}Pu. His value is 2000 rem per μCi initially deposited in the lung, a value which should, to be consistent with usage elsewhere in this document, be changed to 4000 rem/μCi (he uses Q=10 for alpha rays whereas 20 should be used because the depth of the relevant tissue is not known and therefore the appropriate LET is not known). The plutonium does not stay long in the lung (200-300 days) but does have a long residence time in the body. One may then take the present body burden as being equal to the initial lung burden.

Of the 26 workers noted above, 11 are stated to have more than 40 nCi and 15 therefore have between 6 and 40 nCi. Taking a crude average based on these data, the mean burden may be 70 nCi. If we assume (as elsewhere here) 1 WLM = 4 rem, 70 nCi (280 rem) is equivalent to 70 WLM. The attributable risk of lung cancer found in various studies ranges from 1 to 30 per 10^6 PY-WLM (Table 5.1). With 70 WLM, 26 persons and 30 years at risk, the range of predicted lung cancers is $(1-30) \times 10^{-6} \times 70 \times 26 \times 30$ or approximately 0.05 to 1.5. Clearly the null result is quite consistent with either extreme, and can only be used as evidence that at low doses even the higher predictions are not wrong by a factor of more than about 5.

In the larger number of persons (224), assuming a body burden of 20 nCi, the expected excess lung cancer on the above-hypotheses ranges from 0.15 to 4.5; adding in the "natural" expected of 3.2, one might expect 3.3 to 7.7 against the 1 observed. This may be the healthy worker effect, but again it indicates that the "predicted" lung cancer attributed risk is not much too low at low doses.

Another comparison can be made with animal studies. Using the review by Bair (Ba74), "significant increases in pulmonary neoplasia occurred at doses of about 30 rads and above". In dogs, nearly all animals which had doses between 1200 and 4000 rads to the lungs had lung tumours. Taking Q = 20, the significant increases occurred at 600 rems, and the dogs quoted above had 24000 to 80,000 rems. The 26 workers with a dose equivalent of 280 rem were thus exposed much below the levels at which excesses were observed in these dogs.

With respect to bone cancer, again using the estimates of Cohen (but using Q = 20 rather than 10), the dose rate to bone is 162 rem/yr per μCi initially in the lung. Again assuming that the (mean) 70 nCi was initially in the lung, this gives 11.2 rem/year. Over 30 years, this gives 336 rems (with a maximum value, in one case, of approximately 1000 rem).

In animals "osteogenic sarcoma has been reported in rats with accumulated mean doses of less than 10 rads" (Ba74), but, as with lung cancer, statistically significant increases have not occurred at less than 30 to 50 rads, i.e. 3000 to 5000 rem (Q = 20, together with a distribution factor of 5 both here and in the rem calculation of the previous paragraph). Thus the dose equivalent of the 26 humans is below the lower edge of "statistically significant" dose equivalent in animals. On the basis of radium data, Mays et al. (BEIR p. 508, #22) accepts a bone sarcoma risk of 6-53 bone sarcomas per 10^6 persons per rad of Ra. Using this value, 336 rem would give a risk of 10^{-4} to 10^{-3} per person; thus bone sarcoma in any of the 26 workers would be unlikely. Again then the data merely states that the estimated risks are not exceedingly low.

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APPENDIX J

STATISTICAL METHODS FOR FITTING DOSE-RESPONSE MODELS

J.1 INTRODUCTION

For purposes of setting standards, it is frequently desired to have estimates of risk in terms of some function of exposure treated as a continuous variable. However, epidemiological data, on which such estimates are to be based, are generally presented in the form of observed and expected events in broad categories of exposure. Recent statistical advances now allow continuous dose-response functions to be fitted directly to individual exposure-outcome data without the intermediate step of grouping (Be80, Th81a), but obviously these methods can only be applied by those with access to the raw data. In attempting to arrive at a synthesis of knowledge from various studies, this review is restricted to the data available in the open literature.

In this appendix, the potential loss of information resulting from grouping is examined empirically on data for which fits to the original ungrouped measurements have already been reported. Next, the weighted least squares procedure used in BEIR80 for fitting dose-response function to cohort data is reviewed and illustrated using the data on lung cancer in the Colorado plateau uranium miners. Since the resulting fit appears to be unsatisfactory, the alternatives of constraining the origin, choosing a more general model, and weighting by dose are considered. Finally it is shown how weighted least squares can be used to combine data from several studies.

J.2 EFFECT OF GROUPING

The possible loss of information involved in fitting models to grouped data will be illustrated empirically on a set of data from a case-control study of lung cancer in a cohort of Quebec asbestos miners (Li77, Th81a). In this study there is considerably more information at low doses than is usually available in studies of radiation effects; indeed 48% of the cohort and 36% of the lung cancer deaths had exposures less than 30 $10^6(p/f^3)$yr=90 (f/l) yr, roughly the maximum possible exposure under the 2 fibre/l occupational standard in force in most places.

Table J.1 gives the matched estimates of relative odds and their geometric standard errors in seven arbitrarily chosen exposure categories, together with the mean exposure in each category. Under the linear dose-response model, it can be shown that the mean relative odds in each category is the same as the relative odds predicted for the mean exposure. For other models, a different measure of "average exposure" would be preferred, but provided the categories were narrow enough, the mean would be a fairly accurate approximation.

Table J.1 also provides the mean risk in each category under the linear hypothesis, (i) as estimated from the raw data (given in (Th81a)) and (ii) as estimated from the grouped data by replacing each individual's actual exposure by the mean in his exposure category. Thus we see that the estimates from the grouped data show a somewhat smaller slope than those based on the original data. This is consistent with the well-known dilution effect of random misclassification for binary data (Co77b); the effect of errors of measurement on continuous exposure data is also to reduce the slope (Ar81) but no quantitative estimates of the magnitude of the effect are yet available. an empirical description of the effect is provided in Table J.2, which relates the amount of downward bias to the number of categories used. Thus, the cruder the grouping, the more the slope is biased downward (except for the 12 categories chosen by "isotonic regression" (Ba72), which gives the best possible fit to a monotonic step function and therefore the steepest slope).

Table J.3 explores the effect of grouping on the ability to choose between various dose-response models. For the ungrouped data, the linear model is clearly favoured over the quadratic (likelihood ratio (LR) χ_1^2 = 0.68 vs 10.26, comparing each against the linear-quadratic mixture). For the grouped data, all the likelihoods are smaller because of the corrupting effect described above, but the LRs comparing models are fairly similar, suggesting either that grouping has little effect on comparisons between models (even though the estimates themselves may be biased) or that we have been lucky for these particular choices of categorizations and models.

Dose-response data can be thought of as having both local and global structure. The fit of a parametric model is determined essentially by the global structure of the data, that is, the closeness of the observed to the predicted results over the entire exposure range, and this global structure is not appreciably affected by local changes like grouping. However, where data in the range of interest (e.g. low doses) is sufficiently rich, it would be desirable to make maximum use of the local structure in that range. The problem with binary outcome data (i.e., risks) is that the results for an individual are so extremely variable (i.e. either zero or one) that they cannot be presented as a scatter diagram, and indeed the only way of visualizing the local structure is by some form of grouping. If the focus of attention is to be the local structure, then such groups must be kept small but then the penalty is greater variability. One way out of the dilemma is to impose a minimal constraint such as monotonicity or piecewise linearity. For radiation, monotonicity may not be valid at high doses because of cell killing effects, but it is probably reasonable for low doses. Under this restriction, it becomes possible to choose a grouping by an iterative search which produces the best fit to a non-decreasing step function (Figure J.1 (Th82)). Thus it is apparent that there is detailed information in these data on the changes in risk of very low doses. Because of its discontinuous nature, such an "isotonic regression" function (Ba72) would be awkward for use in setting standards, but it provides an attractive means of visualizing the fit of a continuous model in the range of interest. Formal LR tests of goodness of fit, using the isotonic regression as an alternative hypothesis, are complicated by the fact that the number of degrees of freedom is also a random variable, but the approach merits further study, particularly for testing fit at low doses.

In summary, grouping causes slope parameters to be slightly underestimated, but has relatively little effect on power to discriminate between models. Some allowance for these effects should be made when presenting models fitted to grouped data, and investigators should be encouraged to fit models directly to their raw data, and to consider their grouped data more in a descriptive and supporting role. One means of presenting grouped data which merits greater use is isotonic regressions.

J.3 METHODS OF FITTING GROUPED DATA

J.3.1. General Approach

Table J.4 illustrates the way results of epidemiological cohort studies are typically presented. The data come from the cohort study of Colorado plateau uranium miners (Ar80). The following discussion of models to fit these data is intended merely to illustrate the methodologic approaches used in the main body of this report.

Let $k = 1, \ldots, n$ subscript the various exposure categories and let z_k be a measure of average exposure in category k (e.g. the mid-point as in Table J.4 or the mean as in Table J.1) let d_k denote the number of deaths (total or cause-specific) observed in the category and e_k the number expected, based on the person-years in view y_k and the age- and sex-specific rates in the reference population (e.g. the total regional population or the entire cohort). Then the usual measures of the effect of exposure are the attributable risk rate $AR_k = (d_k - e_k)/y_k$ and the relative risk $RR_k = d_k/e_k$. Table J.4 expresses these per unit of exposure, i.e. $10^6 AR_k/z_k$ and $10^2(RR_k - 1)/z_k$. The two measures differ only by the multiplicative factor $10^4 e_k/y_k$ describing the crude death rate expected in each group. Thus, dose-response models could be expressed equivalently in terms of either parameter of effect, but the relative risk model has the advantage of being independent of any age differences between groups.

Let $r(z,\underline{\beta})$ be some specific mathematical model which we wish to fit to the observed relative risks RR_k, where $\underline{\beta}$ is a vector of unknown parameters to be estimated from the data. The choice of models might have been deduced from theoretical considerations or inferred by examining plots of data and is not considered further here. It is desirable to construct a general multiparameter model which includes all possibilities under consideration, thus allowing the fits of specific submodels against the more general alternative (Th81a). For example, the general model

$$r(z,\underline{\beta}) = \beta_0\ (1+\beta_1 z + \beta_2 z^2)\ \exp(-\beta_3 z - \beta_4 z^2) \qquad [1]$$

considered in BEIR80 includes both the linear (no "threshold") and quadratic ("threshold") models as special cases in which $\beta_2 = 0$ or $\beta_1 = 0$ respectively.

Thus for any specific model, we see the value $\hat{\underline{\beta}}$ for which the predictions $\hat{r}_k = r(z_k,\hat{\underline{\beta}})$ are "overall as close" to the RR_k as possible. Two criteria for judging overall closeness which are commonly used are maximum likelihood (ML)

$$\min_{\underline{\beta}} \left\{ L(\underline{\beta}) = \prod_k \text{Prob}\ (RR_k \mid \hat{r}_k) \right\} \qquad [2]$$

and weighted least squares (WLS)

$$\max \left\{ WSS = \sum_k (RR_k - \hat{r}_k)^2\ w_k \right) \qquad [3]$$

where w_k are weights based on the precision of $\hat{r}_k$, i.e. $w_k = 1/\sigma^2(\hat{r}_k)$. For binary data, it can be shown (Co70) that the two criteria are equivalent; the following development will be expressed in terms of weighted least squares, for which computer programs are widely available (e.g. Statistical Analysis System (SAS79) procedure NLIN or Biomedical (BMDP79) programs P3R or PAR). The same approach is used in the BEIR80 analysis of the atomic bomb data.

It is convenient to re-express the WLS criterion in terms of the observed counts d_k as follows

$$WSS = \sum_k (d_k - \hat{d}_k)^2\ w'_k \qquad [4]$$

where $\hat{d}_k = e_k\hat{r}_k$ and $w'_k = 1/\sigma^2(\hat{d}_k)$. Assuming the d_k follows a Poisson process, $\sigma^2(\hat{d}_k) = \hat{d}_k$ so equation [4] is simply a chi-square on n-p degrees of freedom where p is the number of parameters being estimated; the minimum value of [4] can thus be used as a test of goodness-of-fit. Note that the weights depend on $\hat{r}_k$, the fitted model, and will change as the estimates of the parameters change. Thus even for the linear model, the derivatives of equation [4] are nonlinear in β and iterative methods must be used to solve them.

J.3.2. Example--Unconstrained fits to the data of Archer et al.

Table J.5 and Figure J.2 provide a summary of the results of fitting various subsets of model [1] to the data of Table J.4 subject to the constraint that $\beta_p \geq 0$ for p=0,...,4. First, it is obvious that none of the pure quadratic models (i.e. those with $\beta_1=0$) fit at all, even with β_3 or β_4 present to avoid overestimation of high doses. In fact when both β_1 and β_2 are allowed into the model, the constraint that $\beta_2 \geq 0$ always forces $\hat{\beta}_2$ to equal zero.

Among the linear models, either β_3 or β_4 may be present, producing virtually indistinguishable results, but to have both would be redundant. While the fit with either present is better than with neither, the improvement in fit is no better than would have been expected by chance (LR $\chi_1^2 = 0.46$, p>.50). However, the overall fit of the linear model is not impressive, either with the exponential term ($\chi_5^2 = 9.58$, p=.09) or without it ($\chi_6^2 = 10.04$, p=.12). Examination of the contributions of each data point to the lack of fit reveals that it is the lowest exposure category for which the fit is the worst; here the predicted relative risk under the linear model is 2.18 (1.90 with the exponential term) in comparison with 0.76 observed (95% confidence interval 0.58, 0.98)). This lack of fit in the lowest category becomes even more worrisome when one notes that the predicted risk of zero exposure is 1.97 (1.64 with the exponential term). This would appear to suggest either (i) a true excess risk among those even trivially exposed, (ii) some selection effect in the opposite direction from that generally observed for occupational cohorts, or (iii) a dilution of the slope resulting from errors in measurement. Whatever the explanation, this curve is clearly unacceptable as a basis for setting standards because it would appear to suggest that any exposure, however small, nearly doubled the risk of lung cancer. Hence, in the next sections we consider various alternative approaches to model fitting.

J.3.3. Alternative 1: Constraining the Origin

An obvious solution would be to declare that at zero dose there should be zero effect, i.e. that $r(0,\underline{\beta}) = \beta_0 = 1$. The result is explored in Table J.6 and Figure J.3. As expected, the slope at low doses β_1 is considerably increased, as is the contribution of the exponential term to avoid overestimation at high doses. Overall the fit is worsened somewhat, but only slightly more than would have to be expected by chance on removing one parameter ($\chi_1^2 = 2.20$, P=.14). The fit is still not impressive ($\chi_6^2 = 11.78$, P=.07), but the contribution of the lowest exposure category to the lack of fit is now considerably reduced.

However, the choice $\beta_0 = 1$ was somewhat arbitrary. Indeed, the usual experience in those occupational mortality studies in which expectations are based on general population rates is that the least exposed show less than expected mortality (i.e. $\beta_0 < 1$) generally though to be due to selective admission of fitter persons into employment (the "healthy worker effect"). Estimates of β_0 from 0.7 to 0.9 are quite commonly reported (McM76), though these vary between causes of death, racial, and age groups. Unfortunately, the estimate of slope β_1 depends fairly strongly on the value β_0 is constrained to and such arbitrariness is undesirable as a basis for setting standards. It is important to note that the choice $\beta_0 = 1$ cannot be considered conservative, as it would underestimate the slope if the healthy workers effect were operating in the cohort.

It is instructive to compare the results for $\beta_0 = 1$ with the *ad hoc* analysis of the same data in the BEIR80. Taking the entire cohort as a single data point produces $d_1 = 159$, $e_1 = 25.24$ and $z_1 = 1180$. Thus taking $\beta_0 = 1$ and setting $r_1 = d_1/e_1 = 6.30 = 1 + \beta_1 z_1$ yields an estimate of $\beta = .0045$ in good agreement with that obtained by WLS in Table J.5 with $\beta_3 = 0$. Obviously, such a procedure would be inadequate if the risks per unit exposure decrease at high doses as they clearly appear to. To remedy this, the calculation was repeated using only the data on those exposed to less than 600 WLM, to arrive at an estimate of $\beta_1 = 0.0080$, now somewhat higher than the 0.0055 value estimated in Table J.5 with $\beta_3 > 0$.

J.3.4. Alternative 2: Other Dose-Response Models:

The observation in Table J.4 that the relative risk per unit of exposure decreases fairly smoothly with increasing dose throughout the exposure range (not merely in the highest categories where cell killing might be expected) suggests that the linear model is inadequate. This has led some authors (Mo78) to suggest the general form

$$r(z,\underline{\beta}) = \beta_0(1+\beta_1 z^{\beta_5}) \exp(-\beta_3 z) \qquad [5]$$

where $\beta_5 < 1$ would be consistent with the effect noted in Table J.4. The results of fitting this model are described in Table J.7 and Figure J.4. First note that allowing β_5 to be less than 1 makes β_3 unnecessary. With β_0 left free, the model failed to converge, as decreasing values of β_5 led to smaller and smaller values of β_0 (unreasonably small) in an attempt to fit the lowest data point. Thus β_0 had to be constrained to some arbitrary value, and for purposes of illustration $\beta_0 = 1$ was chosen. The fundamental problem with this model is that for $\beta_5 < 1$, the slope at zero dose becomes infinite. (This is the real reason for the failure to converge.) If biologically correct, this would imply that any exposure beyond background was dangerous however slight. This problem might be remedied by assuming that occupational exposure acts in combination to other unmeasured factors β_6 to be estimated, i.e.

$$r(z,\underline{\beta}) = \beta_0[1 + \beta_1(z+\beta_6)^{\beta_5}] \qquad [6]$$

However, attempts to fit this model have led to zero estimates of $\hat{\beta}_6$, even with constraints on β_0 and β_5. Other families of sublinear curves with finite slope at zero dose should therefore be sought.

J.3.5. Alternative 3: Weighting Low Dose Data More Heavily

Obviously if the interest of regulatory bodies is in the low-dose range, then data in this range should in some sense carry heavier weight than that in the high dose range, particularly if the effects are expected to differ. The approach taken in the BEIR80 essentially gives equal weight to all data up to 600 WLM and zero weight thereafter. A more sensible approach would be to replace the weights in equation [4] by $w'_i = f(z_k)/\hat{d}_k$ where $f(z_k)$ is some smoothly decreasing function of exposure. Table J.8 and Figure J.5 describe the results for three choices of f which span the range which might be chosen. Like the constraint on β_0 discussed above, the choice is arbitrary and has a considerable influence on the results, but unlike the situation for β_0, no single choice of weights is particularly "natural". Leaving β_0 free, one might prefer the weights which produce estimates of $\hat{\beta}_0$ closest to unity, but of course this criterion merely replaces one form of arbitrariness by another.

J.3.6. Synthesis

Any combination of these approaches could be used. Based on the results of Tables J.5 to J.8 and invoking a large measure of subjective judgement a best estimate of the relationship for this data might set the model [5] with β_0 constrained to the interval [0.8, 1.0] and with weighting function $f(z)=1/\sqrt{z}$. The resulting dose-response curve is plotted in Figure J.6 and is compared with the unconstrained linear-exponential and constrained linear models. This model describes the low-dose relationship well, but there is bound to be quarrel with the choices made. However, it is better to base an analysis on specifically stated assumptions (even if arbitrary) than on either hidden or biased ones. This analysis offers a purely statistical critique of the data of Archer et al. and, it should be emphasized, takes no account of its methodological limitations or its concordance with the results of other studies.

J.3.7. Pooling Results from Several Studies

In arriving at a judgement on risks based on the current state of knowledge, the usual practice is to report a range of predictions from different studies (eliminating those judged to be methodologically unsound). While this range is certainly important to have, there remains a need to describe the "best" point estimate of risk. Obviously in the first step, the results of each study would have to be examined separately, in terms of their methodologic validity and the extent to which a common form of dose-response relationship might be fitted. For purposes of illustration, suppose it would appear that a linear relationship might fit all studies, but with differences in slope and/or intercept. Let $j=1,\ldots,J$ subscript the studies and $i=1,\ldots,n_j$ the groups used within each study, and let d_{ij}, e_{ij} and z_{ij} be as defined earlier. Then four models might be chosen for pooling:

$$r(z,\underline{\beta}) = \beta_{0j}\,(1 + \beta_{1j}z) \tag{7.1}$$

$$r(z,\underline{\beta}) = \beta_{0j}\,(1 + \bar{\beta}_1 z) \tag{7.2}$$

$$r(z,\underline{\beta}) = \bar{\beta}_0\,(1 + \beta_{1j}z) \tag{7.3}$$

$$r(z,\underline{\beta}) = \bar{\beta}_0\,(1 + \bar{\beta}_1 z) \tag{7.4}$$

Each model could be fit by WLS as described earlier. Appropriate comparisons between models would then provide a specific test of the equality of slopes and intercepts, as in the analysis of covariance (Sn67). If either were judged to be essentially similar, pooling would be appropriate, whereas if they differed, pooling might be misleading. However the main interest is in the slope parameter β_1, as differences in β_0 might well be anticipated from variation in, say, the strength of the healthy worker effect. Thus model [7.2] would be quite suitable for setting standards even if [7.4] were rejected. On the other hand if only [7.1] or [7.3] fit adequately, results would have to be reported in terms of the range of estimates of $\hat{\beta}_{1j}$.

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TABLE J.1

Effect of Grouping on Risk Estimates Under the Linear Model

(Data on Lung Cancer in Relation to Asbestos Exposure from Th81a)

Exposure Category	Mean Exposure	Matched Estimates of Relative Odds		
		Observed	Fitted to Linear Model	
			Individual Data	Grouped Data
0 - 9	3	1.00	1.01	1.01
10 - 99	43	1.12	1.10	1.08
100 - 599	274	1.54	1.61	1.53
600 - 999	752	2.60	2.67	2.46
1000 - 1499	1207	3.61	3.68	3.35
1500 - 2999	2093	5.46	5.66	5.07
3000 +	3592	5.39	8.99	7.98

TABLE J.2

Effect of Grouping on Slopes and Standard Errors of Linear Relationships

(Data on Lung Cancer in Relation to Asbestos Exposure from Th81a)

Number of Categories	Estimate of Slope	Standard Error of Slope
None	.00222	.00068
12*	.00266	.00077
7	.00194	.00062
3	.00185	.00062

* Chosen by isotonic regression

TABLE J.3

Effect of Grouping on Ability of LR Tests to Discriminate Between Models

(Data on Lung Cancer in Relation to Asbestos Exposure from Th81a)

Model	Data	Likelihood Ratios Relative to	
		Null hypothesis	Linear-Quadratic Hypothesis
Linear	Individual	35.63	0.68
	Grouped	30.49	0.18
Quadratic	Individual	26.06	10.26
	Grouped	23.11	7.56
Linear-Quadratic	Individual	36.31	--
	Grouped	30.68	--

TABLE J.4

Lung Cancer Risks in U.S. Uranium Miners (Ar80)

Cumulative WLM		Person-years	Lung cancers		Absolute risk, cases per 10^6 PY per WLM	Relative risk, % increased risk/WLM
Range	Midpoint		Observed	Expected		
0-119	60	5,183	3	3.96	—	—
120-239	180	3,308	7	2.24	8.0	1.2
240-359	300	2,891	9	2.24	7.8	1.0
360-599	480	4,171	19	3.33	7.8	1.0
600-839	720	3,294	9	2.62	2.7	0.3
840-1,799	1,320	6,591	40	5.38	4.0	0.5
1,800-3,719	2,760	5,690	49	4.56	2.8	0.4
>3,719	7,000(est.)	1,068	23	0.91	3.0	0.3
All	1,180(mean)	32,196	159	25.24	3.52	0.45

TABLE J.5

Fit of Model [4] to Grouped Data in Table A2.4

$\hat{\beta}_0$	$10^3\hat{\beta}_1$	$10^7\hat{\beta}_2$	$10^5\hat{\beta}_3$	$10^9\hat{\beta}_4$	χ^2(df)	P
1.97	1.79	0	0	0	10.04 (6)	.123
1.82	2.12	0	0	3.44	9.93 (5)	.077
1.64	2.78	0	5.26	0	9.58 (5)	.088
4.20	0	1.45	0	0	22.71 (6)	.001
3.28	0	4.54	0	23.10	16.22 (5)	.006
3.21	0	9.10	25.84	0	16.20 (5)	.006

TABLE J.6

Effect of Constraining β_0 on Fit of Model [4]

$\hat{\beta}_6$	$10^3\hat{\beta}_1$	$10^5\hat{\beta}_3$	χ^2(df)	P
1.64	2.78	5.26	9.58 (5)	.088
1.97	1.79	0*	10.04 (6)	.123
1.00*	5.53	8.70	11.78 (6)	.067
1.00*	4.35	0*	16.85 (7)	.018
0.65*	9.50	10.72	14.03 (6)	.029

* constrained parameter

TABLE J.7

Effect of Adding Exponential Parameter (Model [5])

$\hat{\beta}_0$	$10^3\hat{\beta}_1$	$\hat{\beta}_5$	χ^2 (df)	P
1.97	1.79	1.000*	10.04 (6)	.123
1.00*	34.9	.724	7.35 (6)	.290
0.60*	92.7	.671	7.08 (6)	.314

* constrained parameter

TABLE J.8

Effect of Weighting by Dose in Fit of Model [4]

Dose Weighting Function	$\hat{\beta}_0$	$10^3\hat{\beta}_1$	$10^5\hat{\beta}_3$	χ^2 (df)	P
1	1.64	2.78	5.26	9.58 (5)	.088
1/ln z	1.25	4.27	8.31	11.09*(5)	.050
$1/\sqrt{z}$	0.68	11.0	17.2	10.99*(5)	.052
1/z	0.26	41.2	33.3	6.23*(5)	.285

*Weighted chi-square

FIGURE J.1

LINEAR AND ISOTONIC REGRESSION MODELS FOR LUNG CANCER RISKS IN QUEBEC ASBESTOS WORKERS

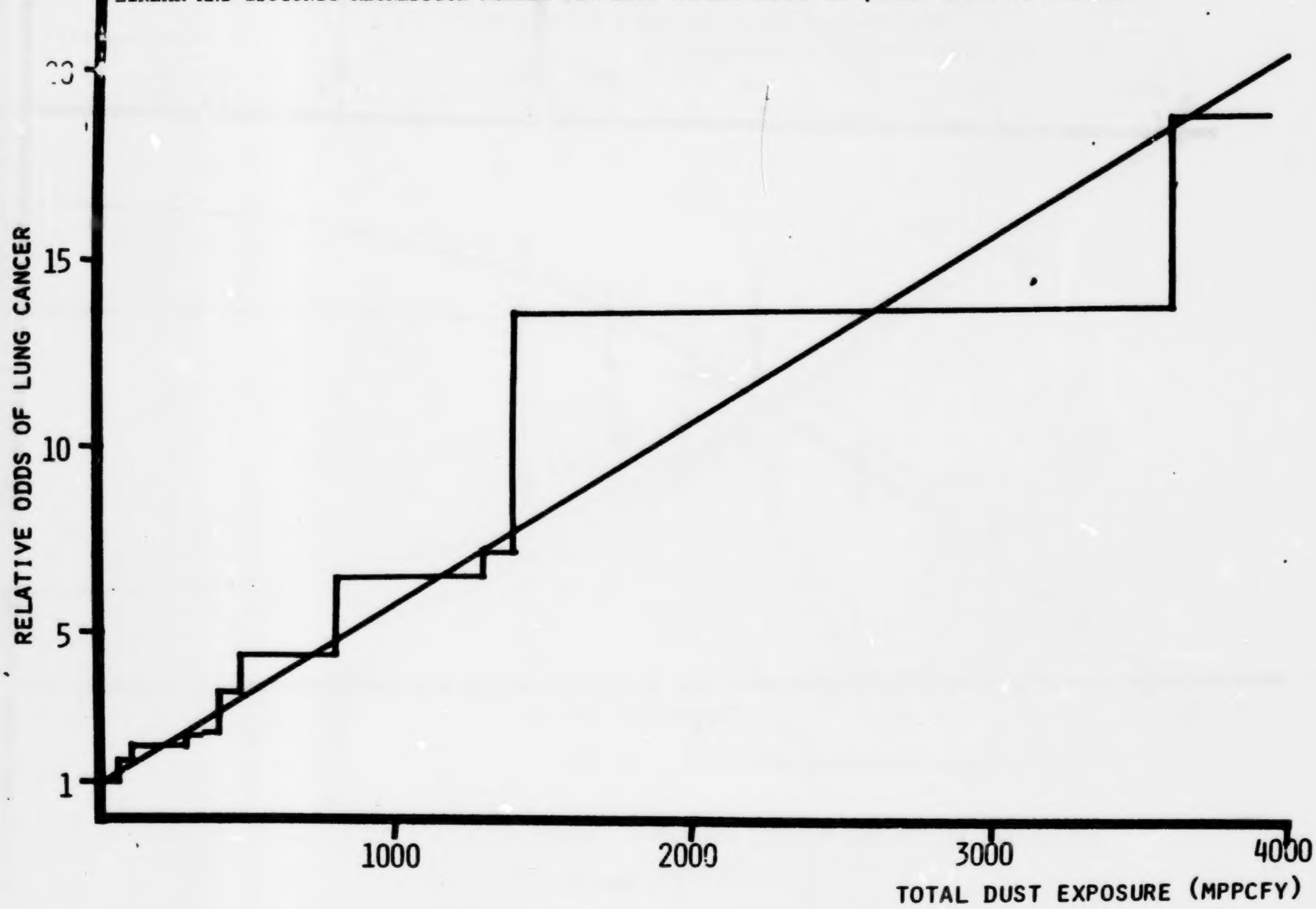
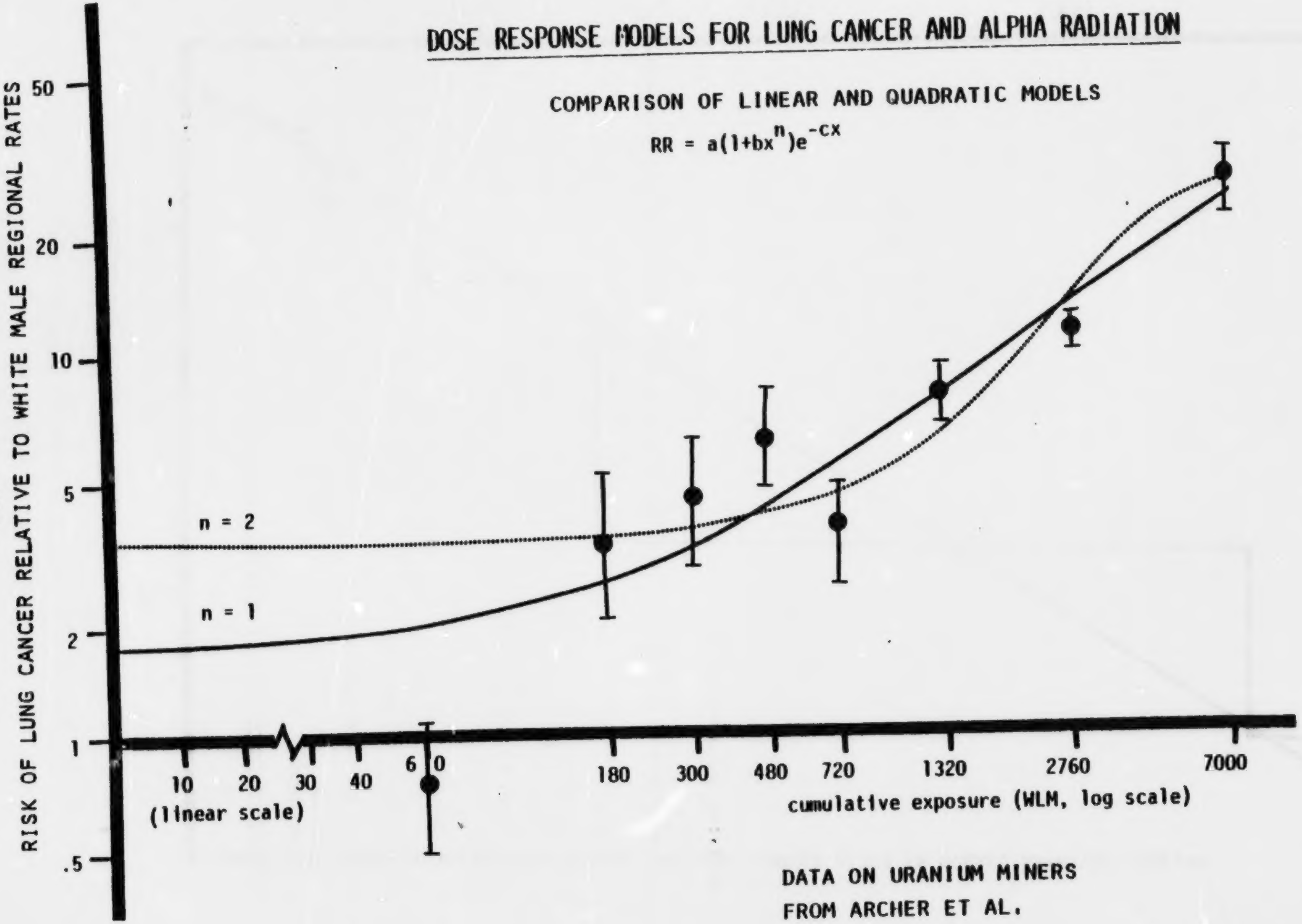


FIGURE J.2

DOSE RESPONSE MODELS FOR LUNG CANCER AND ALPHA RADIATION

COMPARISON OF LINEAR AND QUADRATIC MODELS

$RR = a(1+bx^n)e^{-cx}$



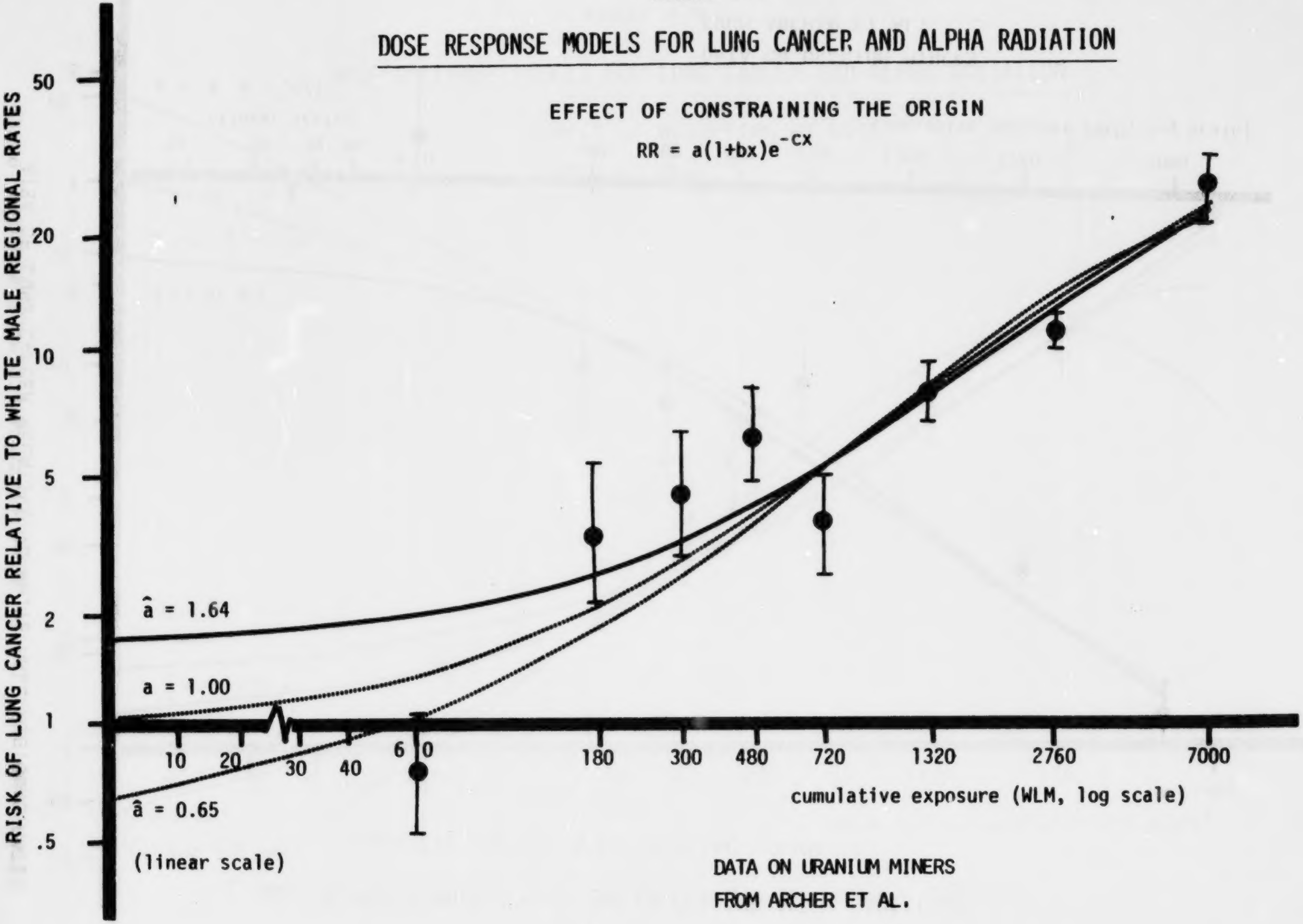
DATA ON URANIUM MINERS
FROM ARCHER ET AL.

FIGURE J.3

DOSE RESPONSE MODELS FOR LUNG CANCER AND ALPHA RADIATION

EFFECT OF CONSTRAINING THE ORIGIN

$RR = a(1+bx)e^{-cx}$



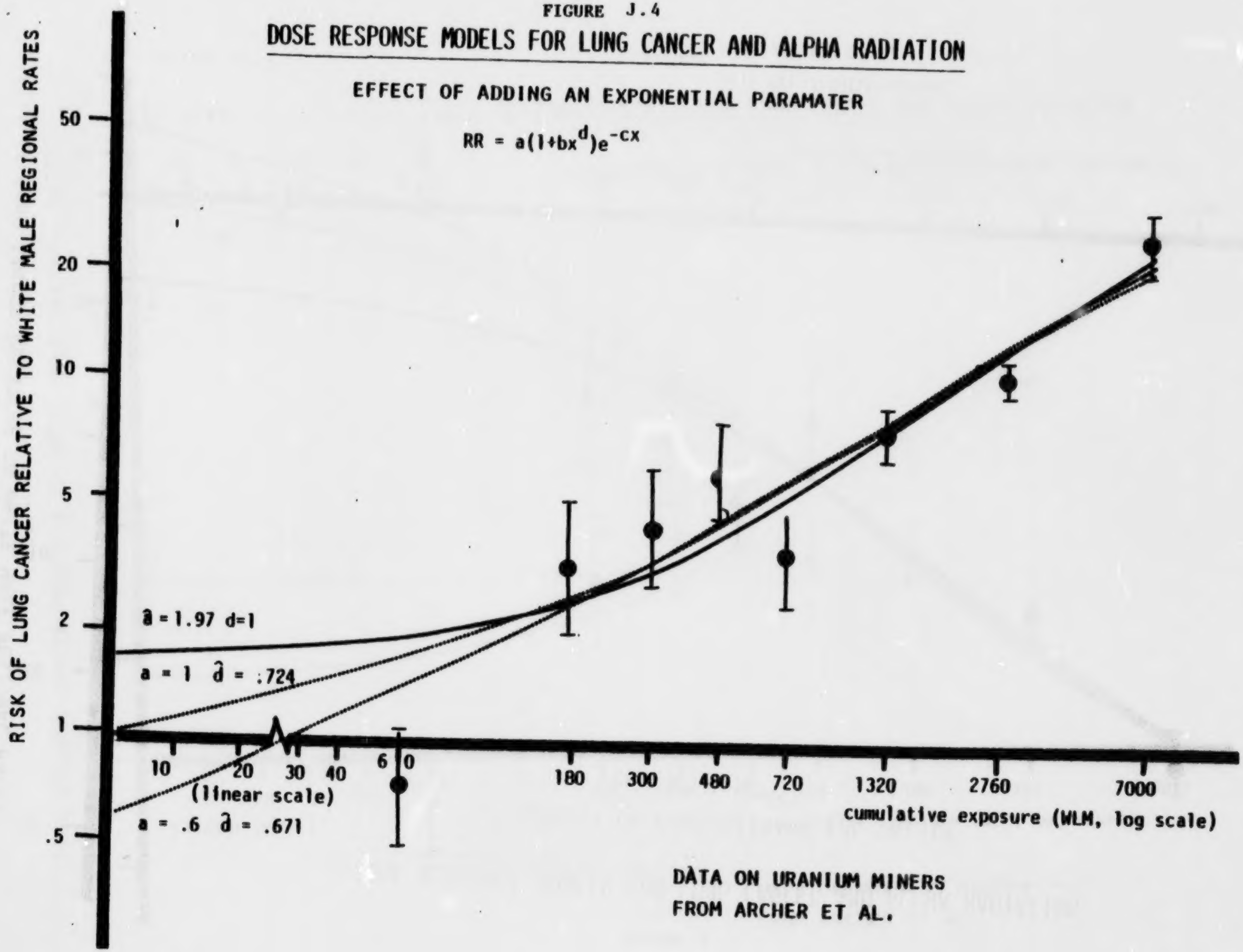
DATA ON URANIUM MINERS
FROM ARCHER ET AL.

FIGURE J.4

DOSE RESPONSE MODELS FOR LUNG CANCER AND ALPHA RADIATION

EFFECT OF ADDING AN EXPONENTIAL PARAMATER

$RR = a(1+bx^{d})e^{-cx}$



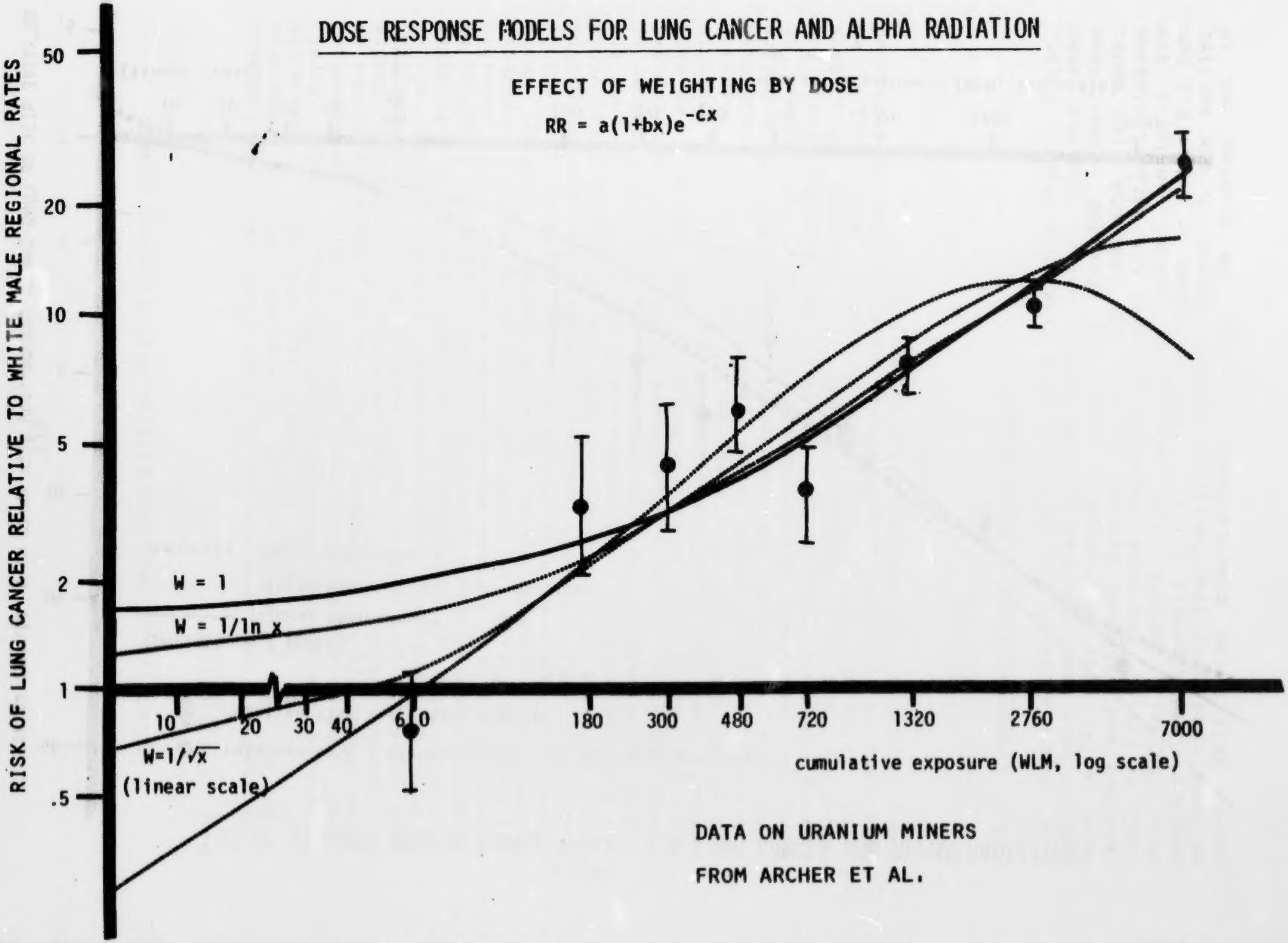
DATA ON URANIUM MINERS
FROM ARCHER ET AL.

FIGURE J.5

DOSE RESPONSE MODELS FOR LUNG CANCER AND ALPHA RADIATION

EFFECT OF WEIGHTING BY DOSE

$RR = a(1+bx)e^{-cx}$

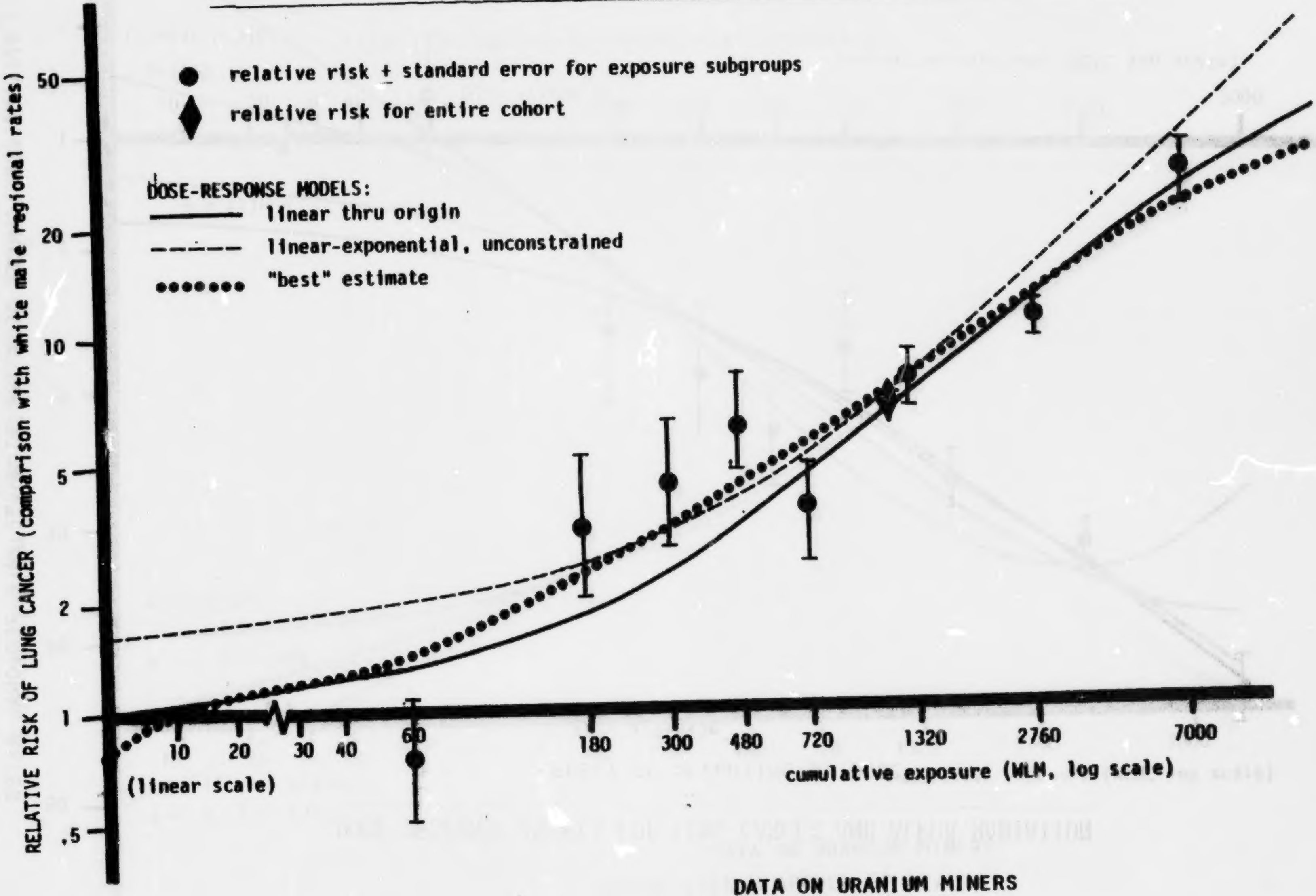


DATA ON URANIUM MINERS

FROM ARCHER ET AL.

FIGURE J.6

FIT OF VARIOUS DOSE-RESPONSE MODELS FOR LUNG CANCER AND ALPHA RADIATION



DATA ON URANIUM MINERS
FROM ARCHER ET AL.

APPENDIX K

SELECTION OF DATA FOR FITTING DOSE-RESPONSE MODELS

K.1 INTRODUCTION

This appendix describes the actual data items selected from each study and any adjustments made to express them in comparable form. Before proceeding to particular studies, it is worth explaining the general principles guiding this process. First, though studies are presented in a variety of ways, the essential items needed for dose-response modelling (see Appendix J) are an estimate of average dose in each category, the number of deaths from the cause of interest, and a measure of the number at risk: persons, person-years, control subjects, expected deaths, etc.-- for uniformity of presentation, we have quoted or estimated expected deaths wherever possible. Second, if not so reported by the investigators, we have attempted to eliminate events observed and expected during the first ten years after start of exposure to deal with latency in a consistent manner. Finally, where groups were small we have pooled to obtain greater statistical stability. This process involves a compromise between having enough subjects in each group (so that the chi square tests would be valid and so that small groups would not unduly influence the fitted relationships) against the need for sufficient number of groups (at least one more than number of parameters in the model being fitted, in most cases a minimum of four groups). We have adopted the "pool adjacent violators" rule for isotonic regression (Ba72) as a consistent policy for doing this: wherever a higher dose group shows lower risks than the next lower dose group, the two groups are combined. In practice, this policy tends to exaggerate the goodness of fit and the degrees of freedom require adjustment. However, we believe that for comparing the fits of competing models, this practice should have little influence on the significance tests. Additionally, we have usually regrouped wherever the number of deaths predicted under linearity fell substantially below five.

K.2 SPECIFIC STUDIES

K.2.1 Czechoslovakian uranium miners

Four issues arise in our choice of data from this study. First, results have been reported for two closing dates. For the later date (Ku79) only attributable risks are provided rather than observed and expected deaths, so only the absolute risk model could be fitted. We have therefore selected the earlier closing date (Ku78a). Second, two methods of cohort analysis are compared (see Appendix I.1.1). Both are given in Table K.1 but we have used only the "original method" (given in the earlier paper, Ku78a) for dose-response fitting. As pointed out in

Appendix I these may overestimate risks at low doses and underestimate them at high doses (En73) but the "modified method" (of Ku78a) has exactly the reverse effect because latency was ignored. We agree with the authors that, while neither is ideal, the bias in the original method is probably less serious in this context because final exposures were attained relatively rapidly. Also because the original method indicates greater convexity (and is therefore "conservative") and because adjustment for latency is possible only for that method (given the data available), we have chosen to use only those results. Third, the authors quote only rates rather than numbers of deaths. However, man-years are provided, allowing the actual numbers to be reconstructed as indicated. (This would not have been possible for the finer breakdown provided in Sv76). Finally, the same adjustment for latency has been applied as was used in BEIR80, namely assuming that one third of the expected deaths occurred in the first ten years after entry in all exposure categories. Thus, for example, in the 400+ category, 10.99/3 = 3.66 deaths are subtracted from both the observed 82 and expected 10.9 figures. The data on age interactions quoted in Table 7.1a come from Ku79, and the data for smoking interactions quoted in Table 7.4 come from BEIR80.

K.2.2 Colorado plateau uranium miners

The basic data used for dose-response fitting comes from the table on p. 384 of BEIR80, which includes mortality to September 1974 with observed and expected deaths in the first ten years after entry already excluded. The only adjustment made is the regrouping of two pairs of small cells as indicated in Table K.2a.

No data on age and latent period interactions have yet been published for the 1974 closing date and the results quoted in Table 7.1 and 7.3 come directly from Tables 2 and 1 respectively of Lu79, based on the 1968 closing date (with only 62 deaths, including those 5 to 10 years after entry). The dose-response age-interaction model for lognormally-weighted "effective" exposure (WLME), quoted in Table 7.2 and used for life table projections, was fitted to the data given in Table K.2b. No cross-tabulations of risk by age and effective exposure have yet been published, but from the data in Table 2 of Lu79, it is evident that the two factors must be considered in combination. To accomplish this, at least approximately, we have combined the data from Table 2 of Lu79 (which gives a breakdown of risks by age over the period from 1960 to 1968) and Table 41 of Lu71 (which gives a breakdown of risks by effective exposure in the same population but from 1950 to 1968). Unfortunately, the latter table provides no information on age, except that on average the population at risk must be younger because follow-up started 10 years earlier. However, mean ages could be inferred by exploiting the relationship between age and the expected death rate (ER, expected deaths divided by person-years) apparent in Table 2 of Lu79. This was done by visually fitting the relationship $ER=aA^b$ and then comparing the expected rates in Table 41 of Lu71 to this curve to infer the mean ages, quoted in Table K.2.b. The resulting models (Table 7.2) must be considered to be only approximate, but are probably more reliable than completely ignoring either age or effective exposure. Some lack of fit must of course be expected because of the crudeness of our way of combining the two data sets; as most subjects appear twice in the table, the formal significance tests and standard errors are of course meaningless, except relatively.

Since lower risks are observed in this study than in others, risk projections based on these fitted models will also be lower. We have therefore scaled the projected risks reported in Table 8.2 upwards in proportion to the ratio of risks between the Czechoslovakia and Colorado plateau studies, derived as follows. For the Czechoslovakia data, our risk indices are $ARI=16.82/10^6$ PY-WLM and $RRI=2.01/10^2$ WLM (Table 8.1), leading to estimated risks at the mean exposure in that study, 313 WLM, of $AR=5265/10^6$ PY and excess RR = 6.29. The Colorado risk indices are expressed in units of WLME, which in that study are equal to 0.045 WLM, so 313 WLM = 14.13 WLME (this ratio would of course vary with age and pattern of exposure). The corresponding age-independent risk estimates for the Colorado study (Table 8.1) are $AR=8.61\times10^{-5}\times14.13^{0.83} = 776/10^6$ PY and excess $RR=0.13\times14.13^{0.87} = 1.30$. Our scaling factors (Footnotes 2 and 3 of Table 8.1) are therefore 5254/776 = 6.78 for projections based on the attributable risk model and 6.29/1.30 = 4.84 for projections based on the relative risk model.

For smoking interactions, the data before reclassification of causes of death quoted in Table 7.6 come from Table 4 of AR76 with minor corrections to the numbers of deaths (V. Archer, personal communication, 1981). For the version after reclassification, only observed deaths and rates are provided in Table 3 of Ar78a. Table K.2c shows how these were manipulated to reconstruct the person-years needed for dose-response modelling. The only serious complication is that in cells with no deaths observed, the person-years are unknown and must be estimated. We have done this by obtaining the marginal distributions in the known cells by smoking, height, and duration-exposure categories, assuming these three factors interacted independently (i.e. multiplicatively), and scaling the predicted person-years in the empty cells so that the total coincided with the person-years quoted in BEIR80 (Table K.2d). These adjustments are rather doubtful, but affect mainly the very low risk categories and thus probably have little influence on the fitted model. It would have been desirable to obtain the original data, but time constraints precluded this.

K.2.3 Ontario uranium miners

The distribution of lung cancer cases and comparison subjects quoted in Table K.3 come from Table C.1 of He76. First we have pooled two sets of categories as indicated because of small numbers. Next we have expressed the distribution of comparison subjects in terms of expected deaths by multiplying each by a constant factor chosen so that the expected number in the lowest category equals the number predicted by the linear model (from C.1). (This sum is in close agreement with the 45.1 estimated on a cohort basis using Ontario rates.) Finally, we have eliminated the 19 cases in the first ten years after entry listed in Table C.4 of He76 from the observed numbers and multiplied the expected deaths in each category by (45.1-19)/45.1. This adjustment is valid only if the categories have comparable age and year of entry distributions. For the lung cancer cases listed in C.4 we could see no consistent pattern of differences in means across these categories so we have some confidence in our adjustment, but obviously the actual distribution of controls would be more reliable.

The data on age interactions quoted in Table 7.1 comes from Table C.3 of He76.

K.2.4 Newfoundland fluorspar miners

The distribution of observed and expected deaths quoted in Table K.4 comes from Table 3 of an unpublished manuscript (dV80). We have also received copies of computer printouts cited in BEIR80 calculated on a slightly different basis but found that the differences had negligible effect on the fitted relations; we have therefore quoted only the version in the manuscript. Here, the expected deaths are based on the age- and year-specific rates in the entire cohort and thus total the observed deaths. These have been rescaled so observed equals expected in the surface workers. As these are a very small number, the resulting expectations are highly unreliable. We have also attempted to estimate an appropriate scaling factor by weighted least squares fitting all the data including the surface workers to a linear model with the intercept left as a free parameter, but encountered convergence problems. We have therefore used the figures quoted in the last column, eliminating the 0-dose group on which the others are constrained. This lack of a suitable basis for estimating expected deaths could lead to erroneous inferences about shapes of dose-response relations, as discussed in Section 4.2.1.1.

The data on age interactions quoted in Table 7.1 comes from Table 4 of the same manuscript.

K.2.5 Swedish metal miners

The data quoted in Table K.5 comes from Sn74. The only manipulation required was to multiply the average number of employees underground by the 11 year period of observation to obtain person-years (not used in the fitting process). As the exposure categories are overlapping, we suspect that they consist of entire mines or other heterogeneous groupings. No data on age, smoking, latency or other effects are reported in this publication.

K.2.6 Atomic bomb survivors

The data on atomic bomb survivors quoted in Table K.6 comes from three Tables in Be78a and one in Ke79 as quoted in BEIR80: the T65 doses (gamma and neutron components, K_γ and K_n respectively, in rads kerma) quoted in Table II, the person-years in Table I, and the observed and expected lung cancers in Table XII. From the T65 doses, we have calculated a dose equivalent in rems as

$$DE = R_1K_\gamma + QR_2K_n + R_3K_n$$

where we have assumed a quality factor Q of 10 for neutrons and R_1, R_2, and R_3 are ratios of tissue absorbed to kerma doses given in Ke79. Next we have combined several categories, particularly at Nagasaki, because of small numbers. Finally, as all expected deaths are based on the entire cohort, we have scaled these so that observed equals expected in the zero dose groups and eliminated those groups from the fitting process. We have also tried estimating the scaling parameter by weighted least squares including the zero rad groups and leaving the intercept as a free parameter. The resulting estimates were not substantially different from unity and produced larger confidence intervals on the other parameters, so for most analyses we have used the expectations quoted in the last column (unlike the Newfoundland miners, these are based on relatively large numbers).

The data on age interactions (Tables 7.1 and 7.3) and latent periods (Table 7.4) come from exactly comparable adaptations of the other breakdowns provided in Tables V (leukemia), VI (all causes other than leukemia), and XII (lung cancer). The data on smoking interactions (Table 7.6) comes from Table 4 of Is75.

K.2.7 Radium dial painters

The data quoted in Table K.7 comes from Tables II and IV of Ro78a. The only adjustments made consist of eliminating the group with less than 0.5 µCi systemic intake (as was done by Ro78a) and regrouping some of the lowest dose categories with fewer than one death predicted (as was done by Ro78a in their goodness of fit testing, but not in their fitting itself). We agree with the authors that systemic intake is a better dose parameter to use for fitting than average skeletal dose because, as it is time invariant, it avoids the bias involved in relating risk to cumulative dose at death (En73) discussed in Sections 6.1.5, I.1.1 and K.1.1.

The data on age interactions quoted in Table 7.3 comes from Table 4 of Po78.

K.2.8 Radium injection patients

The data quoted in Table K.8 were obtained by tabulating the detailed listings of cases at risk (Appendix B of Sp78) and sarcomas (Tables 1 and 2 of Ma78) into the same categories used in their earlier publication Sp70. The more detailed age breakdown provided in Table 7.3 comes from Table 5 of Sp70. The data on protraction effects plotted in Figure 7.4 comes from Table 3 of Ma78, who also provide a figure giving an even more detailed breakdown by injection span.

K.2.9 Animal data on bone sarcoma

Table K.9 (a-c) gives the raw data from the various animal studies summarized in Table 6.2 as used by the fitting program, together with the number of cases predicted by the linear cell killing model ("PREDCT"), the observed cumulative incidence ("CUM INC") and its 95% confidence intervals, and the predicted cumulative incidence ("RISK") as plotted in Figure 6.1. Doses are given in rads average skeletal dose if a constant multiple of injected dose or in μCi of actual injected dose otherwise.

Only the data on neptunium require particular comment. The numbers of rats at risk (i.e. surviving the minimum latent period) were inferred from the numbers of rats treated and the percentage incidence by finding the largest integer less than or equal to the number treated which could reproduce the indicated percentage; where the percentage was zero, the average ratio of surviving to treated animals was used. The data were then grouped as indicated to eliminate the very small cells. Method of application, chemical form, and sex variables were included in the analysis as described in Section 6.2.2.

The data on protraction effects plotted in Figure 7.3 comes from Table 2 and 3 of Mu78

K.2.10 Animal data on skin cancer

Table K.10 gives the data from Tables I and IV of Bu68 in the same format as the data on skin cancer, with one important difference: the column headed "SARCOMA" is in fact the total number of skin tumors, not the number of animals affected. Thus the other derived columns "CUM INC" and "RISK" are average numbers of tumors per rat rather than risks. However, as discussed in Section 6.1.5, it is meaningful to relate these directly to dose in view of relation [6.1], and no complementary exponential transformation is needed as was used in fitting the bone sarcoma data.

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TABLE K.1

RAW DATA ON CZECHOSLOVAKIAN URANIUM MINERS

Exposure Category	Mean	Person Years	Lung Cancer Deaths					
			Observed			Expected		
			Risk per 10,000 py	Number Total	Number 10+ yrs[1] after entry	Rate per 10,000 py	Number	Number 10+ yrs[1] after entry
Original Method								
0-99	74	4,072	14.7	6	4.97	7.6	3.09	2.06
100-199	150	15,234	26.3	40	36.04	7.8	11.88	7.92
200-399	290	22,165	37.9	84	78.53	7.4	16.40	10.93
400+	570	15,484	52.9	82	78.34	7.1	10.99	7.33
Modified Method								
0-99	74	9,380	6.4	6	NE	5.5	5.16	NE
100-199	150	16,131	24.8	40	NE	7.6	12.26	NE
200-399	290	19,614	42.8	84	NE	7.7	15.10	NE
400+	570	11,830	69.3	82	NE	8.4	9.94	NE

Source: Ku 78a

Notes: [1] Assuming one third of expected deaths occurred in the first 10 years after entry (see BEIR80).
NE Not estimable because person-years would be accumulated at different times after first exposure in the different exposure categories.

TABLE K.2a

RAW DATA ON COLORADO PLATEAU URANIUM MINERS

Exposure Category	Mean	Person-Years	Lung Cancer Deaths	
			Observed	Expected
0-119 120-239	60) 180) 103	5183) 3308) 8491	3) 7) 10	3.96) 2.24) 6.20
240-359	300	2891	9	2.24
360-599 600-839	480) 720) 586	4171) 3294) 7465	19) 9) 28	3.33) 2.62 5.95
840-1799	1320	6591	40	5.38
1800-3719	2760	5690	49	4.56
3719+	7000	1068	23	0.91

Source: Archer *et al* (unpublished) as quoted in BEIR80.

TABLE K.2b

RAW DATA ON COLORADO PLATEAU URANIUM MINERS IN RELATION TO LOG-NORMALLY WEIGHTED EFFECTIVE EXPOSURE

Source	Exposure		Age		Person years	Lung Cancers	
	Range WLM	Mean WLME	Range	Median		Observed	Expected
Lu71	0-360	6.241	--	42.1[1]	17,872	13	4.38
	360-839	27.103	--	44.0[1]	9,046	14	2.95
	840-1799	63.317	--	45.1[1]	6,607	12	2.52
	1800-3719	126.116	--	45.7[1]	3,455	21	1.43
	3720-	319.971	--	46.0[1]	978	10	0.42
Lu79	--	48.784	35-44	40.0	6,834	3	0.85
	--	52.381	45-49	47.5	3,182	16	1.61
	--	55.722	50-54	52.5	2,921	11	2.88
	--	50.667	55-59	57.5	1,964	16	3.85
	--	53.159	60-64	62.5	1,055	7	2.76
	--	54.494	65-69	67.5	599	6	3.28
	--	29.702	70-	75.0	323	3	1.28

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[1] Estimated by fitting a power function to the expected rates as a function of age in Lu79 and comparing the expected rates quoted in Lu71.

TABLE K.2c
RAW DATA ON SMOKING-RADIATION INTERACTIONS FROM Ar78a

Inferred person years are given in handwritten figures. (Figures in brackets are estimated from the marginal distributions.)

TALL WORKERS (70 or more inches in height)

Years after Start of Underground Uranium Mining	Cigaret Usage	Non-Cigaret Smokers			Light (Less than 19 Cigarets/day)			Moderate (20 Cigarets per day)			Heavy (More than 20 Cigarets/day)			Former Smokers		
	Working Level Months	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
0-4.9	Bronchogenic Cancers	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
	Cases/1000 PY	-	-	-	-	-	-	0.82	-	-	-	5.33	-	-	-	-
5-9.9	Bronchogenic Cancers	0	0	0	0	0	0	0	0	2	0	0	0	0	1	1
	Cases/1000 PY	-	-	-	-	-	-	-	-	10.31	-	-	-	0	2.96	21.12
10-14.9	Bronchogenic Cancers	0	0	0	2	0	0	3	1	1	2	1	0	1	0	0
		[512]	[313]	[459]	472	[222]	[322]	1277	1149	322	524	568	[249]	140	[290]	[419]
	Cases/1000 PY	-	-	-	4.24	-	-	2.35	0.87	3.11	3.82	1.76	-	7.14	-	-
15 or more	Bronchogenic Cancers	0	1	1	1	3	2	2	8	11	2	7	13	0	1	4
		[573]	595	435	364	536	223	791	1436	1120	368	844	494	[530]	388	316
	Cases/1000 PY	-	1.68	2.30	2.75	5.60	8.97	2.53	5.57	9.82	5.43	8.29	26.33	-	2.58	12.65

MEDIUM HEIGHT WORKERS (68.0-69.9 inches)

Years after Start of Underground Uranium Mining	Cigaret Usage	Non-Cigaret Smokers			Light (Less than 19 Cigarets/day			Moderate (20 Cigarets per day)			Heavy (More than 20 Cigarets/day)			Former Smokers		
	Working Level Months	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
0-4.9	Bronchogenic Cancers	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	Cases/1000 PY	-	-	-	2.94	-	-	-	-	-	-	-	-	-	-	-
509.9	Bronchogenic Cancers	0	0	0	0	1	0	1	1	0	1	0	0	0	0	0
	Cases/1000 PY	-	-	-	-	5.76	-	1.44	1.62	-	3.00	-	-	-	-	-
10-14.9	Bronchogenic Cancer	0	1	0	1	0	0	0	2	1	0	5	0	0	1	1
		[278]	319	[241]	325	[118]	[171]	[592]	699	181	[276]	320	[222]	[122]	146	67
	Cases/1000 PY	-	3.13	-	3.08	-	-	-	2.86	5.54	-	15.62	-	-	6.85	14.95
15 or more	Bronchogenic Cancer	0	1	0	0	1	3	0	9	7	1	5	3	1	1	3
		[304]	455	[132]	[216]	246	198	[606]	985	625	220	478	141	36	225	224
	Cases/1000 PY	-	2.20	-	-	4.07	15.17	-	9.14	11.02	4.55	10.46	21.28	27.46	4.45	13.38

SHORT WORKERS (less than 68 inches)

Years after Start of Underground Uranium Mining	Cigaret Usage	Non-Cigaret Smokers			Light (Less than 19 Cigarets/day)			Moderate (20 Cigarets Per day)			Heavy (More than 20 Cigarets/day)			Former Smokers		
	Working Level Months	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
0-4.9	Bronchogenic Cancers	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Cases/1000 PY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5-9.9	Bronchogenic Cancers	0	0	0	0	0	0	2	3	1	0	0	0	0	0	1
	Cases/1000 PY	-	-	-	-	-	-	3.39	4.92	10.74	-	-	-	-	-	41.60
10-14.9	Bronchogenic Cancers	0	0	1	0	1	1	1	4	2	0	1	1	0	1	1
		[204]	[112]	65	[121]	204	25	500	650	128	[186]	197	26	[82]	109	31
	Cases/1000 PY	-	-	14.76	-	4.89	40.47	2.00	6.15	15.68	-	5.08	38.28	-	9.14	32.32
15 or more	Bronchogenic Cancers	0	0	0	1	1	1	0	8	9	0	3	4	1	1	2
		[300]	[311]	[127]	224	282	88	[607]	914	359	[180]	174	143	105	155	42
	Cases/1000 PY	-	-	-	4.46	3.54	11.32	-	8.75	25.09	-	17.22	28.00	9.49	6.47	47.26

TABLE K.2d

SUMMARY OF RAW DATA ON SMOKING-RADIATION INTERACTIONS FROM TABLE K.2c

Radiation Category	Smoking Category	Lung Cancers	Person Years
Low - 10+ years	never	0	2143
	light, med, former	14	6892
	heavy	5	1763
10-14 years Med-High	never	2	1507
	light, med, former	17	5253
	heavy	8	1752
15+ years Med	never	2	1089
	light, med, former	33	5167
	heavy	15	1496
15+ years High	never	1	750
	light, med, former	42	3205
	heavy	20	778
All	All	159	31,795

TABLE K.3

RAW DATA FOR ONTARIO URANIUM MINERS

Exposure Category	Mean	Lung Cancer Cases		Comparison Subjects	Expected Lung Cancer Deaths	
		All	10+ years after entry		All[2]	10+ years after entry[3]
0	0) 10	1) 30	21	4) 48	26.20	15.16
1-30[1]	10)	29)		44)		
31-59	40	17	14	20	10.92	6.32
60-89	70) 85	9) 14	10	4) 8	4.37	2.53
90-119	100)	5)		4)		
120+	190	20	17	5	2.73	1.53

Source: He76

Notes

[1] As per He76 Table C.4. Note discrepency with He76 Table C.1.

[2] Proportional to the numbers of comparison subjects, but scaled so the lowest category equals the number of cases expected under the linear hypothesis.

[3] Assuming the 19 observed cases in years 0-9 are the same proportion of the number expected (45.1) in each exposure category.

TABLE K.4

RAW DATA ON NEWFOUNDLAND FLUORSPAR MINERS

Exposure category	Mean	Lung Cancer Deaths		
		Observed	Expected[1], relative to	
			Total Cohort	Surface Workers
0	0	6	27.11	6.00
1 - 119	60	5	22.53	4.99
120 - 239	180	5	7.53	1.67
240 - 359	300	7	4.27	0.94
360 - 479	420	11	2.87	0.63
480 - 599	540	9	2.32	0.51
600 - 719	660) 720	7) 9	1.28) 2.19	0.48
720 - 839	780)	2)	0.91)	
840 - 959	900) 960	6) 9	0.74) 1.09	0.24
960 - 1079	1020)	3)	0.35)	
1080+	1750[2]	10	1.06	0.23

Source: de Villiers and Wigle (unpublished)

Notes:

[1] Based on age- and year-specific rates in the entire cohort, and scaled so observed equals expected for the unexposed group.

[2] Estimated.

TABLE K.5

RAW DATA ON SWEDISH METAL MINERS

Exposure Category	Mean	Person Years[1]	Lung Cancer Deaths	
			Observed	Expected
2-36	15	11,011	2	1.25
13-112	48	20.372	7	2.31
48-528	218	16.368	15	1.85
170-1512	696	5,775	12	0.66

Source: Sn73

[1] Average number of employees underground times 11 years in view.

TABLE K.6

RAW DATA ON ATOMIC BOMB SURVIVORS

City	T65 Doses (Rads Kerma)			Dose Equivalent (Rems)[1]	Person Years	Lung Cancer Deaths		
	Range	Mean Gamma	Mean Neutron			Observed	Expected based on	
							Entire Cohort	0 Rad Subgroup
Hiroshima	0	0.0	0.0	0.0	630,100	105	126.0	105.0
	1-9	2.9	0.8	3.3	291,900	55	57.6	48.0
	10-49	17.6	4.3	18.6	227,500	57	46.9	39.1
	50-99	56.8	13.4	58.8	56,900	16	12.5	10.1
	100-299	130.4	37.7	150.8	49,900	17	11.0	9.2
	300+	327.0	122.1	440.7	18,400	7	3.4	2.8
Nagasaki	0	0.0	0.0	0.0	101,200	16	18.7	16.0
	1-99	36.9	0.1	18.6	251,100	41	43.9	37.6
	100+	237.4	3.5	126.6	60,800	16	10.4	8.9

Source: Be78a

Notes: [1] Assuming Q=10 and organ dose estimates from Ke79.

TABLE K.7

RAW DATA FOR THE RADIUM DIAL PAINTERS

Systemic Intake (µCi)		Person Years at Risk[1]	Number of tumors
Range	Weighted mean		
Bone Sarcoma			
0.5–49	6	19,449	0
50–99	68	977	0
100–249	171	1,164	2
250–499	375	1,249	9
500–999	675	610	8
1000–2499	1675	419	15
2500+	3802	219	4
Head Carcinoma			
0.5–24	4	16,147	0
25–99	49	2,219	2
100–249	176	945	5
250–499	366	812	5
500–999	584	275	2
1000+	1577	164	3

Source: Ro78a

[1] Person-years in view less 5 years per subject (bone sarcoma) or 10 years per subject (head carcinoma).

TABLE K.8

RAW DATA FOR THE RADIUM INJECTION PATIENTS

Average Skeletal Dose (Rads)		Injected Patients[1]	Bone Sarcomas[2]
Range	Weighted Mean[1]		
Juveniles			
0-199	113	12	0
200-499	363	35	2
500-999	727	73	6
1000-1999	1345	70	19
2000-5750	3329	21	8
Adults			
0-89	53	194	0
90-199	139	206	3
200-499	309	192	6
500-999	650	53	4

Source: Ma78 and Sp78

[1] From detailled listing in appendix B of Sp78

[2] From detailled listing in Tables 1 and 2 of Ma78

TABLE K.9a

RAW DATA ON BONE SARCOMAS IN BEAGLES
Source Ma72

a. ^{226}Ra

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.058	12	0	0.885	0.00000	-0	0.14785	0.07371
0.156	14	1	2.723	0.07143	-0	0.27877	0.19450
0.330	13	5	4.628	0.38462	0	0.64458	0.35603
1.070	12	11	8.757	0.91667	1	1.16793	0.72977
3.210	13	12	12.434	0.92308	1	1.03396	0.95650
10.410	10	9	8.903	0.90000	1	1.09370	0.89030

b. ^{228}Ra

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.018	12	0	0.886	0.00000	-0.14792	0.14792	0.07380
0.050	10	0	1.931	0.00000	-0.24464	0.24464	0.19306
0.148	10	5	4.475	0.50000	0.19181	0.80819	0.44753
0.309	9	7	6.041	0.77778	0.47194	1.08361	0.67569
0.973	9	9	8.177	1.00000	0.81168	1.18832	0.90856
2.620	5	4	4.558	0.80000	0.55121	1.04879	0.91163
8.400	4	1	0.861	0.25000	-0.15271	0.65271	0.21516

c. ^{228}Th

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.002	13	0	0.589	0.00000	-0	0.11307	0.04532
0.005	12	0	1.573	0.00000	-0	0.14094	0.13106
0.015	12	2	4.051	0.16667	-0	0.43422	0.33755
0.030	13	10	7.249	0.76923	0	1.03922	0.55761
0.042	13	12	11.814	0.92308	1	1.07958	0.90880
0.290	12	12	11.939	1.00000	1	1.04028	0.99490
0.850	4	2	2.034	0.50000	0	0.99993	0.50838
2.700	2	0	0.000	0.00000	-0	0.00000	0.00000

d. ^{239}Pu

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.016	14	4	3.922	0.28571	0	0.52095	0.28016
0.048	14	9	8.780	0.64286	0	0.89616	0.62714
0.104	12	10	10.257	0.83333	1	1.03271	0.85475
0.296	12	12	11.948	1.00000	1	1.03713	0.99568
0.909	12	12	12.000	1.00000	1	1.00288	0.99997
2.880	9	7	6.993	0.77778	1	1.04975	0.77696

TABLE K.9b

RAW DATA ON BONE SARCOMAS IN MICE

e. ^{226}Ra in female CFI mice (F169a)

OSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.050	254	11	5.859	0.04331	0.02485	0.06177	0.02307
0.100	252	5	8.680	0.01984	-0.00267	0.04236	0.03444
0.250	247	19	16.682	0.07692	0.04563	0.10822	0.06754
0.500	683	80	81.565	0.11713	0.09281	0.14145	0.11943
0.750	504	94	84.432	0.18651	0.15390	0.21911	0.16754
1.000	239	56	50.712	0.23431	0.18247	0.28614	0.21218
[illegible]	104	22	[illegible]	0.21154	0.13791	0.28516	0.25366
2.500	104	45	43.866	0.43269	0.33778	0.52761	0.42179
5.000	45	28	28.247	0.62222	0.48098	0.76347	0.62771
10.000	43	34	34.580	0.79070	0.67209	0.90931	0.80419
20.000	44	38	39.301	0.86364	0.77238	0.96489	0.89321
40.000	45	33	39.564	0.73333	0.63811	0.82855	0.87920
80.000	44	31	26.973	0.70455	0.56063	0.84846	0.61301
120.000	45	14	12.498	0.31111	0.18025	0.44197	0.27773

f. ^{239}Pu in female CFI mice (F169a)

OSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
0.040	99	0	2.273	0.00000	-0.02950	0.02950	0.02296
0.080	96	0	3.311	0.00000	-0.03650	0.03650	0.03449
[illegible]	77	3	4.300	0.03896	-0.01288	0.09080	0.05712
0.340	87	7	9.228	0.08046	0.01575	0.14517	0.10607
0.690	40	7	7.745	0.17500	0.05255	0.29745	0.19362
1.700	28	12	11.064	0.42857	0.24749	0.60965	0.39513
3.100	26	20	14.938	0.76923	0.57919	0.95928	0.57465
6.300	13	9	9.517	0.69231	0.45156	0.93305	0.73210
15.600	15	6	6.122	0.40000	0.15127	0.64873	0.40816

g. ^{224}Ra in female NMRI mice

OSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
00.000	138	0	1.802	0.00000	-0.01894	0.01894	0.01306
50.000	140	0	1.865	0.00000	-0.01899	0.01899	0.01332
00.000	244	3	4.374	0.01230	-0.00435	0.02894	0.01792
75.000	50	2	1.587	0.04000	-0.00859	0.08859	0.03174
50.000	145	19	10.478	0.13103	0.08798	0.17409	0.07571
25.000	148	13	24.611	0.08784	0.02785	0.14783	0.16629
10.000	148	26	[illegible]	[illegible]	[illegible]	[illegible]	0.17600
5.000	148	25	19.110	0.16892	0.11489	0.22294	0.12912
2.500	200	17	16.632	0.08500	0.04673	0.12327	0.08316
1.000	200	16	8.925	0.08000	0.05138	0.10862	0.04463

h. ^{224}Ra in male NMRI mice

E	AT RISK	SARCOMA	PREDCT				
00	138	0	0.002	0.00000	-0.00062	0.00062	0.00001
00	140	0	0.122	0.00000	-0.00488	0.00488	0.00087
00	244	4	3.375	0.01639	-0.00071	[illegible]	0.01599
250	50	2	2.035	0.04000	-0.01477	0.09477	0.04070
00	145	1	10.151	0.07586	0.03433	0.11739	0.07001
50	148	9	10.279	0.06081	0.01985	0.10177	0.06945
0	148	5	[illegible]	[illegible]	[illegible]	0.0443[illegible]	[illegible]
50	148	4	2.985	0.02703	0.00438	0.04968	0.02017

TABLE K.9c

RAW DATA ON BONE SARCOMAS IN MICE AND RATS

i. ^{224}Ra (single injection) in female NMRI mice (Mu78)

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
1500	92	13	8.267	0.14130	0.08287	0.19974	0.08986
1080	50	4	7.108	0.08000	-0.01680	0.17680	0.14215
~~750~~	~~93~~	~~10~~	~~17.388~~	~~0.10753~~	~~0.02829~~	~~0.18677~~	~~0.18697~~
360	49	11	9.797	0.22449	0.11250	0.33648	0.19994
300	92	14	17.531	0.15217	0.07192	0.23243	0.19055
150	91	14	12.570	0.15385	0.08295	0.22474	0.13813
~~75~~	~~200~~	~~21~~	~~17.636~~	~~0.10500~~	~~0.06570~~	~~0.14430~~	~~0.08818~~
30	200	14	9.344	0.07000	0.04075	0.09925	0.04672

j. ^{224}Ra (single injection) in male NMRI mice (Mu78)

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
1500	93	6	6.075	0.06452	0.01430	0.11474	0.06532
750	94	7	6.632	0.07447	0.02270	0.12623	0.07055
~~300~~	~~98~~	~~3~~	~~3.497~~	~~0.03061~~	~~-0.00611~~	~~0.06734~~	~~0.03568~~
150	97	2	1.801	0.02062	-0.00624	0.04748	0.01856

k. ^{227}Th (single injection) in female NMRI mice (Mu78)

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
10000	100	60	46.643	0.60000	0.50222	0.69778	0.46643
5000	100	44	64.994	0.44000	0.34651	0.53349	0.64994
~~2000~~	~~100~~	~~47~~	~~58.149~~	~~0.47000~~	~~0.37331~~	~~0.56669~~	~~0.58149~~
1000	100	60	42.807	0.60000	0.50302	0.69698	0.42807
200	100	22	13.347	0.22000	0.15334	0.28666	0.13347
100	100	9	7.528	0.09000	0.03829	0.14171	0.07528
~~20~~	~~100~~	~~3~~	~~2.344~~	~~0.03000~~	~~0.00022~~	~~0.05978~~	~~0.02344~~

l. ^{237}Np in Wistar rats (La72)

DOSE	AT RISK	SARCOMA	PREDCT	CUM INC	95% CONFIDENCE INVERVAL		RISK
3	222	5	1.627	0.02252	0.01130	0.03374	0.00733
18	117	4	7.141 11.01	0.03419	-0.00919	0.07757	0.06103
~~18~~	~~116~~	~~2~~ 11	~~2.237~~	~~0.01724~~	~~-0.00779~~	~~0.04227~~	~~0.01928~~
113	21	4	5.569	0.19048	0.00167	0.37928	0.26520
113	19	10	8.212	0.52632	0.30356	0.74907	0.43224
54	43	6	4.081	0.13953	0.05193	0.22714	0.09491
~~49~~	~~39~~	~~7~~	~~7.665~~	~~0.17949~~	~~0.05477~~	~~0.30421~~	~~0.19654~~
89	20	2 45	2.217 44.79	0.10000	-0.03760	0.23760	0.11086
89	24	4	4.659	0.16667	0.00842	0.32491	0.19413
25	38	0	0.824	0.00000	-0.04630	0.04630	0.02168
~~25~~	~~33~~	~~1~~	~~1.302~~	~~0.03030~~	~~-0.03612~~	~~0.09672~~	~~0.03946~~
520	20	8	8.329	0.40000	0.18395	0.61605	0.41643
520	20	15	12.563	0.75000	0.53819	0.96181	0.62817
231	40	8	9.504	0.20000	0.06810	0.33190	0.23761
~~300~~	~~32~~	~~13~~	~~13.523~~	~~0.40625~~	~~0.23510~~	~~0.57740~~	~~0.42260~~
408	24	5	5.350	0.20833	0.04181	0.37485	0.22293
408	18	5	6.674	0.27778	0.05464	0.50092	0.37079
126	38	5	3.162	0.13158	0.04377	0.21939	0.08320
~~126~~	~~36~~	~~5~~	~~5.309~~	~~0.13889~~	~~0.02306~~	~~0.25472~~	~~0.14748~~

P.b.

TABLE K.10

RAW DATA ON SKIN TUMORS IN RATS

Source: Bu68

[illegible]	AT RISK	[illegible]	[illegible]	CUM INC	95% CONFIDENCE INTERVAL		RISK
210	8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
70	8	1	[illegible]	0.13004	[illegible]	[illegible]	[illegible]
80	1	1	14.402	[illegible]	[illegible]	[illegible]	[illegible]
10	[illegible]	43	[illegible]	1.59024	1.17151	[illegible]	[illegible]
50	20	[illegible]	[illegible]	2.25014	1.77976	2.72062	[illegible]
80	[illegible]	27	[illegible]	0.93007	0.45746	[illegible]	[illegible]
60	9	22	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	7	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	8	7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	9	4	2.976	0.45011	[illegible]	[illegible]	[illegible]

APPENDIX L

LIFE TABLE PROJECTION OF RISKS

L.1 LIFE TABLE CALCULATIONS FOR LUNG CANCER IN THE GENERAL POPULATION

Table L.1 describes life table calculations based on the Canadian male death rates for 1978. These calculations form the basis for comparison with the other risk projections described below, all of which were generated using the same computer algorithm. Thus, for the general population we assume zero exposure beyond natural background (column 2) and the excess risk coefficient (column 3) is therefore irrelevant. The age specific death rates (columns 4 and 5) for lung cancer, m_t^{LC}, and (column 6) all other causes, m_t^{O}, can then be used to compute the five-year probability of dying (column 7) as

$$ {}_5q_t = 1 - \exp(-5(m_t^{LC} + m_t^{O})) $$

except in the last interval, where ${}_{\infty}q_{85} = 1$. Now starting with a population at risk at age 15 of 100,000 persons, the number alive at the start of each interval, (column 8) is simply

$$ \ell_t = \ell_{t-5}(1 - {}_5q_{t-5}). $$

The deaths during each interval are then distributed between causes in proportion to their rates, so the lung cancer deaths (column 9) are

$$ {}_5d_t^{LC} = \ell_t \, {}_5q_t \, m_t^{LC}/(m_t^{LC} + m_t^{O}). $$

Finally, the total of the person-years contributed in each interval (column 10),

$$ {}_5L_t = \ell_t \, {}_5q_t/m_t $$

divided by the initial population 100,000 gives the expectation of life at age 15, namely 56.13 more years. The differences in the total lung cancer deaths and expectations of life comparing each set of assumptions to these population figures forms the basis of the Tables 8.2 and 8.4.

L.2 LIFE TABLE CALCULATIONS FOR LUNG CANCER IN RELATION TO RADON DAUGHTERS

L.2.1 Calculations ignoring smoking

To evaluate the lifetime risks of lung cancer for various assumptions about radon daughter exposures and their effects, we have carried out life table calculations (Tables L.3.a to L.3.z) which are exactly like those described above except for columns 2 to 4. Column 2 describes the effective dose of the midpoint of each age interval resulting from the postulated exposure pattern. This has been evaluated for two exposure patterns, each with four indices of effective dose.

Exposure patterns:

1. An additional 4 WLM per year beyond normal background levels between ages 15 and 64 at active breathing rates; and

2. An additional 0.01 WL beyond normal background levels for 17 hours per day from birth to death at quiescent breathing rates. Assuming quiescent breathing rates confer 1/2 the effective dose of active breathing rates (Section 7.5), this would produce an annual exposure rate of 0.01 WL × 0.5 × 17 hours/day × 365 days/year/(170 hours/working-month) = 0.183 WLM/year.

These exposure rates are then accumulated into total effective doses at each age (column 2) by making one of the following assumptions about the interval over which each increment of exposure has its effect.

Indices of effective exposure

1. Each exposure increment is assumed to have the same effect at all subsequent points in time. Cumulative dose is then computed as

   $$D_t = c(\min(t,t_1)-t_0)$$

   where c is the annual exposure rate, t is the midpoint of the age-at-risk interval, t_0 is the age at first exposure and t_1 is the age at last exposure.

2. Same as exposure index 1 except that the effect is assumed to begin 10 years after each increment of exposure.

3. Each exposure increment is assumed to have the same effect at all points in time from 5 to 25 years later and no effect outside that window. Cumulative dose is then computed as

   $$D_t = \left\{\begin{array}{ll} 0 & t<t_0+5 \\ (t-t_0-5)c & t_0+5<t<t_0+25 \\ 20c & t_0+25<t<t_0+25 \\ (t_1+25-t)c & t_1+5<t<t_1+25 \\ 0 & t_1+25<t. \end{array}\right.$$

4. Each exposure increment is assumed to have an effect at each instant Δt later, having an intensity given by the lognormal distribution with median $\mu = 10$ years and dispersion factor of $e^{\sigma}=1.5$, that is

$$d(\Delta t) = c(2\pi)^{-1/2}(\sigma\Delta t)^{-1} \exp[-\tfrac{1}{2}(\ln(\Delta t/\mu)/\sigma)^2].$$

The cumulative dose at time t is then

$$D_t = \int_{t_0}^{\min(t,t_1)} d(t-\tau)d\tau$$

and the average effective dose over the interval [T,T+5] is

$$\bar{D}_T = \frac{1}{5}\int_T^{T+5} D_t dt.$$

These indices of cumulative exposure are then combined with various relative and attributable risk estimates (column 3) to compute the age-specific lung cancer death rates (columns 4 and 5). The attributable risk model is

$$M_t^{LC} = m_t^{LC} + ARI_t D_t$$

and the relative risk model is

$$M_t^{LC} = m_t^{LC}(1+RRI_t D_t)$$

where ARI_t and RRI_t are estimates of the attributable and excess relative risk per unit exposure (Section 4.1.1) derived from the epidemiological literature, m_t^{LC} are the lung cancer risks in the general population used above and M_t^{LC} are the predicted total radiation-induced and natural lung cancer death rates used in all subsequent life table calculations. The risk indices may depend on age and, in the case of the lognormal indices, on dose. The actual values used in the calculation and the source of these estimates are given in Table 8.1. No epidemiologic studies have been reported using the 10 year lag or 5-25 year window index, so we have used the same risk indices as for accumulation over the entire period. The extent to which this may have caused the risk coefficient to have been underestimated is explored in Table L.2, which gives cumulative WLM-years under the three indices from 10 years after first exposure to close of follow-up for various hypothetical patterns of exposure and lengths of follow-up. The ratios vary over a considerable range, but taking the set of exposure and follow-up durations to be reasonably representative of realistic possibilities, we have adopted the means of the ratios as our adjustment factors for use in Table 8.3.

The calculations in columns 5 to 9 are carried out exactly as described in Section L.1 and the differences in lung cancer deaths and expectations of life are summarized in Table 8.2.

L.2.2 Calculations for comparison industries

Additional lifetables are provided for occupational accidents (Table L.4) and for lung cancer in asbestos miners (Table L.5). To avoid reformatting the life table, deaths and rates for occupational accidents are included in the corresponding columns for lung cancer. Calculations for asbestos exposure are carried out exactly as described above, except that only the relative risk model for exposure accumulated over the entire period is relevant.

L.2.3 Calculations incorporating smoking

As it is now well established that smoking interacts multiplicatively with age effects, there remain four possible forms of interaction of radiation with smoking and age effects: Additive with age and smoking--

$$M_t^{LC} = m_t^{LC*}(1 + RRI_S s) + ARI_R d_t$$

Additive with age, multiplicative with smoking--

$$M_t^{LC} = m_t^{LC*}(1 + RRI_S s) + (1 + RRI_S s)ARI_R^* d_t$$

Multiplicative with age, additive with smoking--

$$M_t^{LC} = m_t^{LC*}(1 + RRI_S s + RRI_R^* d_t)$$

Multiplicative with age and smoking--

$$M_t^{LC} = m_t^{LC*}(1 + RRI_S s)(1 + RRI_R d_t)$$

A range of estimates of RRI_S has been provided, but for illustrative purposes we have selected the figure 13.0 from the studies of British doctors and of Canadian veterans (as quoted in SG79). ARI_R and RRI_R are the same attributable and excess relative risk indices for radon daughters used in the calculations described above; for simplicity we have restricted these calculations to the age-invariant estimates for exposures accumulated over the entire period. ARI_R^*, RRI_R^*, and m_t^{LC*} are not directly estimable from the available data. Instead, we have adjusted the values ARI_R, RRI_R and m_t^{LC} so that the average rate in the combined smoking and nonsmoking populations would be the same as before. Thus, adopting 0.4 as the prevalence of smoking among Canadian males (SG79), the combined rate among those not exposed to radiation is

$$m_t^{LC} = m_t^{LC*}\ (1 + 0.4 \times 13)$$

so

$$m_t^{LC*} = m_t^{LC}/6.2.$$

Use of these rates leads to the life tables for the general populations of smokers and nonsmokers given in Table L.6. In a similar way, it can be show that $ARI_R^* = ARI_R/6.2$ and $RRI_R^* = 6.2RRI_R$. These risk indices for radiation effects among smokers and non-smokers are given in column 3 of Tables L.7.a to L.7.h and the resulting excess lung cancer death rates under the corresponding models are given in column 5. The remaining calculations are as described earlier except that the smoking and non-smoking subpopulations start at 40,000 and 60,000 respectively. As the two subpopulations are decremented at different rates, the total lifetime risk in the combined groups is not identical to that calculated earlier ignoring smoking, even though the average rates are identical. some further refinement might be obtained by using different death rates for all other causes of death, but this is likely to have only a minor effect on the additional lung cancer deaths and loss of life expectancy attributable to radiation.

L.3 LIFE TABLE CALCULATIONS FOR RADIUM IN DRINKING WATER

L.3.1 Effect of ^{224}Ra

Table L.8 describes risk calculations for life-time exposure to drinking water at the Canadian maximum acceptable concentration for ^{224}ra of 111 pCi/ℓ. At two liters per day in adults, this corresponds to 0.0810 μCi per year, or half that figure in children (assuming water consumption proportional to body mass). The percentages absorbed to the blood are guestimates based on ICRP assumptions, which are in turn based on limited animal data. The percentages deposited from blood to bone are the same as those used in calculating doses in the German radium injection study on which our risk coefficients are based; these are also based on ICRP assumptions. The skeletal masses are assumed to be 10% of body mass at all ages; as we have assumed water intake to be proportional to body mass, the effects of these two assumptions cancel out. Average equilibrium skeletal doses are then calculated as described in footnote 3. These multiplied by the risk coefficients (from Section 5.2.5) give the bone sarcoma rate per year. Since we are assuming these are proportional to equilibrium dose, they do not vary within age group and elaborate life-table calculations are not required. Multiplying the rate by the years at risk (assuming a 73 year lifetime) then gives cumulative risk in each age group, whose sum appears in Table 8.6. This risk is so small that the effect on life expectancy is negligible.

L.3.2 Effect of ^{226}Ra and ^{228}Ra

Table L.9 describes life table calculations for life-time exposure to drinking water at the Canadian maximum acceptable concentrations for ^{226}Ra or ^{228}Ra. Again at two liters per day in adults, this corresponds to 0.0189 μCi per year. Assuming twenty percent of this is absorbed into blood in adults (as above) yields a systemic intake of 0.0038 μCi per year. In children, we assume absorption is inversely related to intake, so the same figure applies; this is an ad hoc assumption for convenience, but has relatively little effect on cumulative dose. This rate multiplied by the midpoint age gives cumulative systemic intake. Obviously this will overestimate the true dose at any point in time as the radium is metabolized, but the risk coefficient is based on cumulative systemic intake and therefore incorporates the effects of metabolism. Thus, these risk coefficients multiplied by the cumulative systemic intakes (lagged 5 or 10 years) give the death rates. These are multiplied by the numbers at risk and the five year interval lengths to give the numbers of radium-induced cancer deaths in the last column (we have ignored mortality from other causes in the first 15 years of life and used the numbers at risk from Table L.1). The total of this column is given in Table 8.6. Again the effect on life expectancy is negligible.

References

SG79 Surgeon General. Smoking and Health. Rockville MD: US dept of Health, Education and Welfare, Office on Smoking and Health, 1979.

TABLE L.1

GENERAL POPULATION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	 LUNG CANCER EXCESS	 OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.000	0.0000000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	0.000	0.0000000	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	0.000	0.0000000	0.000003	0.000000	0.00151	0.00755	98145.	1.	488176.
30-34	0.000	0.0000000	0.000007	0.000000	0.00158	0.00791	97405.	3.	485096.
35-39	0.000	0.0000000	0.000047	0.000000	0.00228	0.01159	96634.	23.	480361.
40-44	0.000	0.0000000	0.000165	0.000000	0.00334	0.01762	95514.	78.	473350.
45-49	0.000	0.0000000	0.000371	0.000000	0.00539	0.02840	93831.	172.	462460.
50-54	0.000	0.0000000	0.000828	0.000000	0.00834	0.04483	91166.	369.	445536.
55-59	0.000	0.0000000	0.001322	0.000000	0.01364	0.07231	87079.	555.	419456.
60-64	0.000	0.0000000	0.002192	0.000000	0.02084	0.10878	80782.	836.	381521.
65-69	0.000	0.0000000	0.002751	0.000000	0.03143	0.15920	71995.	904.	330492.
70-74	0.000	0.0000000	0.003821	0.000000	0.04814	0.22880	60533.	1018.	266543.
75-79	0.000	0.0000000	0.003850	0.000000	0.07570	0.32817	46683.	741.	192584.
80-84	0.000	0.0000000	0.003948	0.000000	0.11794	0.45634	31363.	464.	117423.
85-99	0.000	0.0000000	0.002197	0.000000	0.21587	1.00000	17051.	172.	78191.
TOTALS								5342.	5613070.

TABLE L.2

RELATION BETWEEN INDICES OF CUMULATIVE EXPOSURE FOR VARIOUS HYPOTHETICAL COHORTS EXPOSED TO A CONSTANT DOSE RATE OF 1 WLM/YEAR

ngth of ployment ears)	Length of follow-up (years)	Cumulative WLM-years (ratio) starting 10 years after first exposure		
		Exposure index accumulated over:		
		Entire Period	5-25 years	10+ years
10	15	50.0 (1.00)	37.5 (0.75)	12.5 (0.25)
	20	100.0 (1.00)	87.5 (0.87)	50.0 (0.50)
	25	150.0 (1.00)	137.5 (0.92)	100.0 (0.67)
	30	200.0 (1.00)	175.0 (0.82)	150.0 (0.75)
	35	250.0 (1.00)	187.5 (0.75)	200.0 (0.80)
20	25	250.0 (1.00)	187.5 (0.75)	112.5 (0.45)
	30	350.0 (1.00)	275.0 (0.79)	200.0 (0.57)
	35	450.0 (1.00)	337.5 (0.75)	300.0 (0.67)
	40	550.0 (1.00)	375.0 (0.68)	400.0 (0.73)
30	35	550.0 (1.00)	387.5 (0.70)	312.5 (0.56)
	40	700.0 (1.00)	475.0 (0.68)	450.0 (0.64)
	45	850.0 (1.00)	537.5 (0.63)	600.0 (0.71)
verage of above ratios		(1.00)	(0.76)	(0.61)

TABLE L.3a

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	3.194	0.0000168	0.000000	0.000054	0.00168	0.00862	100000.	27.	497842.
20-24	4.106	0.0000168	0.000001	0.000069	0.00206	0.01062	99138.	35.	493053.
25-29	5.019	0.0000168	0.000003	0.000084	0.00151	0.00797	98085.	43.	488471.
30-34	5.931	0.0000168	0.000007	0.000100	0.00158	0.00840	97304.	52.	484475.
35-39	6.844	0.0000168	0.000047	0.000115	0.00228	0.01216	96486.	78.	479491.
40-44	7.756	0.0000168	0.000165	0.000130	0.00339	0.01826	95313.	140.	472200.
45-49	8.669	0.0000168	0.000371	0.000146	0.00539	0.02911	93572.	238.	461018.
50-54	9.581	0.0000168	0.000828	0.000161	0.00834	0.04560	90848.	434.	443805.
55-59	10.494	0.0000168	0.001322	0.000177	0.01369	0.07313	86706.	626.	417476.
60-64	11.406	0.0000168	0.002192	0.000192	0.02084	0.10963	80365.	904.	379372.
65-69	12.319	0.0000168	0.002751	0.000207	0.03193	0.16007	71554.	971.	328305.
70-74	13.231	0.0000168	0.003821	0.000223	0.04814	0.22966	60100.	1070.	264497.
75-79	14.144	0.0000168	0.003850	0.000238	0.07570	0.32897	46298.	780.	190889.
80-84	15.056	0.0000168	0.003948	0.000253	0.11794	0.45703	31067.	488.	116249.
85-99	15.969	0.0000168	0.002197	0.000269	0.21587	1.00000	16869.	190.	77260.
TOTALS								6080.	5594399.

EXCESS DEATHS 738. (13.82%)
LIFE EXPECTANCY LOST 0.1867 YEARS

TABLE L.3b

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	EXCESS	OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	2.281	0.0000168	0.000000	0.000038	0.00168	0.00855	100000.	19.	497862.
20-24	3.194	0.0000168	0.000001	0.000054	0.00206	0.01054	99145.	27.	493110.
25-29	3.650	0.0000168	0.000003	0.000061	0.00151	0.00785	98100.	31.	488574.
30-34	3.650	0.0000168	0.000007	0.000061	0.00158	0.00821	97330.	33.	484651.
35-39	3.650	0.0000168	0.000047	0.000061	0.00228	0.01140	96531.	52.	479776.
40-44	3.650	0.0000168	0.000165	0.000061	0.00339	0.01792	95382.	107.	472625.
45-49	3.650	0.0000168	0.000371	0.000061	0.00534	0.02870	93673.	200.	461610.
50-54	3.650	0.0000168	0.000828	0.000061	0.00834	0.04512	90984.	395.	444579.
55-59	3.650	0.0000168	0.001322	0.000061	0.01369	0.07260	86879.	579.	418429.
60-64	3.650	0.0000168	0.002192	0.000061	0.02084	0.10905	80572.	857.	380470.
65-69	3.650	0.0000168	0.002751	0.000061	0.03193	0.15946	71785.	927.	324981.
70-74	3.650	0.0000168	0.003821	0.000061	0.04814	0.22903	60338.	1031.	265647.
75-79	3.650	0.0000168	0.003850	0.000061	0.07570	0.32838	46519.	751.	191878.
80-84	3.650	0.0000168	0.003948	0.000061	0.11794	0.45651	31243.	469.	116957.
85-99	3.650	0.0000168	0.002197	0.000061	0.21587	1.00000	16980.	176.	77845.
TOTALS								5654.	5603488.

EXCESS DEATHS 312. (5.84%)
LIFE EXPECTANCY LOST 0.0958 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

EXCESS DEATHS 412. (7.71%)
LIFE EXPECTANCY LOST 0.1265 YEARS

TABLE L.3c

HOUSEHOLD EXPOSURE TO .01 W. 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.168	0.0001178	0.000000	0.000020	0.00168	0.00845	100000.	10.	497884.
20-24	0.179	0.0001166	0.000001	0.000021	0.00206	0.01038	99155.	11.	493196.
25-29	0.181	0.0001162	0.000003	0.000021	0.00151	0.00765	98125.	12.	488749.
30-34	0.182	0.0001162	0.000007	0.000021	0.00158	0.00801	97375.	14.	484921.
35-39	0.182	0.0001161	0.000047	0.000021	0.00228	0.01170	96594.	33.	480142.
40-44	0.182	0.0001161	0.000165	0.000021	0.00339	0.01773	95464.	88.	473079.
45-49	0.182	0.0001161	0.000371	0.000021	0.00539	0.02850	93772.	181.	462146.
50-54	0.183	0.0001161	0.000828	0.000021	0.00834	0.04493	91099.	378.	445186.
55-59	0.183	0.0001161	0.001322	0.000021	0.01369	0.07241	87006.	563.	419083.
60-64	0.183	0.0001161	0.002197	0.000021	0.02084	0.10887	80706.	844.	381142.
65-69	0.183	0.0001161	0.002751	0.000021	0.03193	0.15929	71919.	915.	330129.
70-74	0.183	0.0001161	0.003821	0.000021	0.04814	0.22888	60463.	1023.	266222.
75-79	0.183	0.0001161	0.003850	0.000021	0.07570	0.32824	46624.	745.	192332.
80-84	0.183	0.0001161	0.003928	0.000021	0.11794	0.45640	31320.	465.	117257.
85-99	0.183	0.0001161	0.002197	0.000021	0.21587	1.00000	17026.	173.	78068.
TOTALS								5454.	5609529.

EXCESS DEATHS 112. (2.09%)
LIFE EXPECTANCY LOST 0.0354 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 6.74

EXCESS DEATHS 754. (14.11%)
LIFE EXPECTANCY LOST 0.2387 YEARS

TABLE L.3d

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	1.369	0.0000168	0.000000	0.000023	0.00168	0.00847	100000.	11.	497880.
20-24	2.281	0.0000168	0.000001	0.000038	0.00206	0.01047	99153.	19.	493166.
25-29	3.194	0.0000168	0.000003	0.000054	0.00151	0.00781	98115.	28.	488658.
30-34	4.106	0.0000168	0.000007	0.000069	0.00158	0.00825	97349.	37.	484734.
35-39	5.019	0.0000168	0.000047	0.000084	0.00228	0.01201	96545.	63.	479822.
40-44	5.931	0.0000168	0.000165	0.000100	0.00339	0.01811	95386.	125.	472597.
45-49	6.844	0.0000168	0.000371	0.000115	0.00539	0.02896	93658.	224.	461478.
50-54	7.756	0.0000168	0.000828	0.000130	0.00834	0.04545	90946.	426.	444315.
55-59	8.669	0.0000168	0.001322	0.000146	0.01369	0.07299	86812.	614.	418020.
60-64	9.581	0.0000168	0.002192	0.000161	0.02084	0.10949	80476.	894.	379925.
65-69	10.494	0.0000168	0.002751	0.000177	0.03193	0.15994	71664.	963.	328833.
70-74	11.406	0.0000168	0.003821	0.000192	0.04814	0.22954	60202.	1063.	264963.
75-79	12.319	0.0000168	0.003850	0.000207	0.07570	0.32887	46383.	776.	191254.
80-84	13.231	0.0000168	0.003948	0.000223	0.11794	0.45695	31129.	486.	116489.
85-99	14.144	0.0000168	0.002197	0.000238	0.21587	1.00000	16905.	189.	77437.
TOTALS								5918.	5599566.

EXCESS DEATHS 576. (10.78%)
LIFE EXPECTANCY LOST 0.1350 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS 950. (17.78%)
LIFE EXPECTANCY LOST 0.2228 YEARS

TABLE L.3e

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	3.194	0.0000000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	4.106	0.0000000	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	5.019	0.0000000	0.000003	0.000000	0.00151	0.00755	98145.	1.	488876.
30-34	5.931	0.0000000	0.000007	0.000000	0.00158	0.00791	97405.	3.	485096.
35-39	6.844	0.0000100	0.000047	0.000068	0.00228	0.01193	96634.	55.	480284.
40-44	7.756	0.0000100	0.000165	0.000078	0.00339	0.01800	95481.	115.	473097.
45-49	8.669	0.0000100	0.000371	0.000087	0.00539	0.02882	93762.	211.	462023.
50-54	9.581	0.0000200	0.000828	0.000192	0.00834	0.04574	91060.	454.	444805.
55-59	10.494	0.0000200	0.001322	0.000210	0.01369	0.07329	86895.	641.	418351.
60-64	11.406	0.0000200	0.002192	0.000228	0.02084	0.10979	80527.	920.	380101.
65-69	12.319	0.0000500	0.002751	0.000616	0.03193	0.16179	71685.	1106.	328579.
70-74	13.231	0.0000500	0.003821	0.000662	0.04814	0.23134	60087.	1184.	264163.
75-79	14.144	0.0000500	0.003850	0.000707	0.07570	0.33054	46186.	867.	190220.
80-84	15.056	0.0000500	0.003948	0.000753	0.11794	0.45839	30920.	543.	115568.
85-99	15.969	0.0000500	0.002197	0.000798	0.21587	1.00000	16747.	229.	76516.
TOTALS								6331.	5598855.

EXCESS DEATHS 989. (18.51%)
LIFE EXPECTANCY LOST 0.1421 YEARS

HOUSEHOLD EXPOSURE TO .01 WL-17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	2.281	0.0000000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	3.194	0.0000000	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	3.650	0.0000000	0.000003	0.000000	0.00151	0.00755	98145.	1.	488876.
30-34	3.650	0.0000000	0.000007	0.000000	0.00158	0.00791	97405.	3.	485096.
35-39	3.650	0.0000000	0.000047	0.000036	0.00228	0.01177	96634.	40.	480323.
40-44	3.650	0.0000100	0.000165	0.000036	0.00339	0.01780	95497.	95.	473221.
45-49	3.650	0.0000100	0.000371	0.000036	0.00539	0.02858	93797.	188.	462250.
50-54	3.650	0.0000100	0.000828	0.000073	0.00834	0.04518	91116.	401.	445211.
55-59	3.650	0.0000200	0.001322	0.000073	0.01369	0.07265	87000.	585.	418999.
60-64	3.650	0.0000200	0.002192	0.000073	0.02084	0.10910	80679.	863.	380967.
65-69	3.650	0.0000200	0.002751	0.000182	0.03193	0.15997	71877.	967.	329804.
70-74	3.650	0.0000500	0.003821	0.000182	0.04814	0.22950	60379.	1064.	265748.
75-79	3.650	0.0000500	0.003850	0.000182	0.07570	0.32878	46522.	774.	191836.
80-84	3.650	0.0000500	0.003948	0.000182	0.11794	0.45684	31226.	483.	116862.
85-99	3.650	0.0000500	0.002197	0.000182	0.21587	1.00000	16961.	185.	77713.
TOTALS								5650.	5608077.

EXCESS DEATHS 308. (5.77%)
LIFE EXPECTANCY LOST 0.0499 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

EXCESS DEATHS 407. (7.62%)
LIFE EXPECTANCY LOST 0.0659 YEARS

TABLE L.38

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.168	0.0000044	0.000000	0.000001	0.00168	0.00836	100000.	0.	497910.
20-24	0.179	0.0000101	0.000001	0.000002	0.00206	0.01029	99164.	1.	493267.
25-29	0.181	0.0000197	0.000003	0.000004	0.00151	0.00756	98144.	3.	488865.
30-34	0.182	0.0000344	0.000007	0.000006	0.00158	0.00794	97402.	6.	485074.
35-39	0.182	0.0000555	0.000047	0.000010	0.00228	0.01164	96628.	27.	480324.
40-44	0.182	0.0000843	0.000165	0.000015	0.00339	0.01770	95503.	85.	473280.
45-49	0.182	0.0001223	0.000371	0.000022	0.00539	0.02851	93813.	182.	462347.
50-54	0.183	0.0001710	0.000828	0.000031	0.00834	0.04498	91139.	383.	445367.
55-59	0.183	0.0002318	0.001322	0.000042	0.01369	0.07251	87039.	572.	419222.
60-64	0.183	0.0003064	0.002192	0.000056	0.02084	0.10903	80728.	857.	381215.
65-69	0.183	0.0003965	0.002751	0.000072	0.03193	0.15951	71927.	932.	330122.
70-74	0.183	0.0005036	0.003821	0.000092	0.04814	0.22915	60454.	1041.	266136.
75-79	0.183	0.0006295	0.003850	0.000115	0.07570	0.32856	46601.	762.	192192.
80-84	0.183	0.0007760	0.003948	0.000142	0.11794	0.45673	31290.	479.	117111.
85-99	0.183	0.0009448	0.002197	0.000172	0.21587	1.00000	16999.	185.	77891.
TOTALS								5517.	5610316.

EXCESS DEATHS 175. (3.27%)
LIFE EXPECTANCY LOST 0.0275 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 6.74

EXCESS DEATHS 1176. (22.02%)
LIFE EXPECTANCY LOST 0.1856 YEARS

TABLE L.3h

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	1.369	0.0000000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	2.281	0.0000000	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	3.194	0.0000000	0.000003	0.000000	0.00151	0.00755	98145.	1.	488876.
30-34	4.106	0.0000000	0.000007	0.000000	0.00158	0.00791	97405.	3.	485096.
35-39	5.019	0.0000100	0.000047	0.000050	0.00228	0.01184	96634.	47.	480305.
40-44	5.931	0.0000100	0.000165	0.000059	0.00339	0.01791	95490.	106.	473161.
45-49	6.844	0.0000100	0.000371	0.000068	0.00539	0.02873	93779.	203.	462129.
50-54	7.756	0.0000200	0.000828	0.000155	0.00834	0.04557	91085.	437.	444968.
55-59	8.669	0.0000200	0.001382	0.000173	0.01369	0.07312	86934.	626.	418579.
60-64	9.581	0.0000200	0.002192	0.000192	0.02084	0.10963	80578.	907.	380378.
65-69	10.494	0.0000500	0.002751	0.000525	0.03193	0.16141	71744.	1077.	328922.
70-74	11.406	0.0000500	0.003821	0.000570	0.04814	0.23099	60164.	1162.	264558.
75-79	12.319	0.0000500	0.003850	0.000616	0.07570	0.33024	46267.	851.	190591.
80-84	13.231	0.0000500	0.003948	0.000662	0.11794	0.45814	30988.	534.	115845.
85-99	14.144	0.0000500	0.002197	0.000707	0.21587	1.00000	16791.	223.	76750.
TOTALS								6179.	5601330.

EXCESS DEATHS 837. (15.66%)
LIFE EXPECTANCY LOST 0.1174 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS 1380. (25.84%)
LIFE EXPECTANCY LOST 0.1937 YEARS

TABLE L.31

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HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

 AGE     TOTAL     RISK,              DEATH RATES             PROBABILITY  ALIVE     LUNG      PERSON
GROUP    DOSE      INDEX          LUNG CANCER          OTHER       OF        AT     CANCER    -YEARS
                               NATURAL      EXCESS                DYING     START    DEATHS

15-19    3.194  0.0201000   0.000000   0.000000   0.00168   0.00835   100000.      0.    497908.
20-24    4.106  0.0201000   0.000001   0.000000   0.00206   0.01028    99165.      1.    493272.
25-29    5.019  0.0201000   0.000003   0.000000   0.00151   0.00755    98145.      2.    488874.
30-34    5.931  0.0201000   0.000007   0.000001   0.00158   0.00741    97405.      4.    485096.
35-39    6.844  0.0201000   0.000047   0.000006   0.00228   0.01162    96634.     26.    480357.
40-44    7.756  0.0201000   0.000165   0.000026   0.00339   0.01775    95510.     90.    473302.
45-49    8.669  0.0201000   0.000371   0.000065   0.00539   0.02871    93815.    201.    462309.
50-54    9.581  0.0201000   0.000828   0.000159   0.00834   0.04559    91121.    440.    445141.
55-59   10.494  0.0201000   0.001322   0.000279   0.01369   0.07360    86967.    670.    418629.
60-64   11.406  0.0201000   0.002192   0.000503   0.02084   0.11101    80566.   1024.    380031.
65-69   12.319  0.0201000   0.002751   0.000681   0.03193   0.16206    71622.   1127.    328238.
70-74   13.231  0.0201000   0.003821   0.001016   0.04814   0.23271    60015.   1275.    263620.
75-79   14.144  0.0201000   0.003850   0.001095   0.07570   0.33184    46049.    937.    189483.
80-84   15.056  0.0201000   0.003948   0.001195   0.11794   0.45958    30768.    591.    114887.
85-99   15.969  0.0201000   0.002197   0.000705   0.21587   1.00000    16628.    221.     76005.
TOTALS
                                                                              6607.   5597145.

EXCESS DEATHS      1265.   ( 23.68%)
LIFE EXPECTANCY LOST   0.1592 YEARS
```

TABLE L.31

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	2.281	0.0201000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	3.194	0.0201000	0.000001	0.000000	0.00206	0.01028	99165.	1.	493271.
25-29	3.650	0.0201000	0.000003	0.000000	0.00151	0.00755	98145.	2.	488874.
30-34	3.650	0.0201000	0.000007	0.000001	0.00158	0.00791	97405.	4.	485096.
35-39	3.650	0.0201000	0.000047	0.000003	0.00228	0.01161	96634.	24.	480361.
40-44	3.650	0.0201000	0.000165	0.000012	0.00339	0.01768	95512.	84.	473326.
45-49	3.650	0.0201000	0.000371	0.000027	0.00534	0.02853	93823.	184.	462597.
50-54	3.650	0.0201000	0.000828	0.000061	0.00834	0.04512	91146.	396.	445370.
55-59	3.650	0.0201000	0.001322	0.000097	0.01369	0.07276	87034.	595.	419157.
60-64	3.650	0.0201000	0.002192	0.000161	0.02084	0.10949	80701.	896.	380981.
65-69	3.650	0.0201000	0.002751	0.000202	0.03143	0.16005	71865.	974.	329755.
70-74	3.650	0.0201000	0.003821	0.000280	0.04814	0.22988	60363.	1089.	265615.
75-79	3.650	0.0201000	0.003850	0.000282	0.07570	0.32912	46487.	792.	191646.
80-84	3.650	0.0201000	0.003948	0.000290	0.11794	0.45713	31187.	494.	116687.
85-99	3.650	0.0201000	0.002197	0.000161	0.21587	1.00000	16930.	183.	77582.
TOTALS								5717.	5607980.

EXCESS DEATHS 375. (7.03%)
LIFE EXPECTANCY LOST 0.0509 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

EXCESS DEATHS 495. (9.27%)
LIFE EXPECTANCY LOST 0.0672 YEARS

TABLE L.3k

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HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

 AGE     TOTAL    RISK.            DEATH RATES             PROBABILITY  ALIVE    LUNG     PERSON
GROUP    DOSE     INDEX        LUNG CANCER        OTHER        OF        AT     CANCER   -YEARS
                            NATURAL    EXCESS                DYING     START   DEATHS

15-19    0.168  0.1625167  0.000000  0.000000  0.00168   0.00835  100000.      0.   497908.
20-24    0.179  0.1612887  0.000001  0.000000  0.00206   0.01028   99165.      1.   493270.
25-29    0.181  0.1609706  0.000003  0.000000  0.00151   0.00755   98145.      2.   488874.
30-34    0.182  0.1608849  0.000007  0.000000  0.00158   0.00741   97405.      3.   485096.
35-39    0.182  0.1608605  0.000047  0.000001  0.00228   0.01160   96634.     23.   480364.
40-44    0.182  0.1608543  0.000165  0.000005  0.00339   0.01765   95513.     80.   473341.
45-49    0.182  0.1608523  0.000371  0.000011  0.00539   0.02845   93828.    177.   462434.
50-54    0.183  0.1608482  0.000828  0.000024  0.00834   0.04495   91158.    380.   445470.
55-59    0.183  0.1608482  0.001322  0.000039  0.01364   0.07249   87061.    571.   419329.
60-64    0.183  0.1608482  0.002142  0.000064  0.02084   0.10906   80750.    860.   381308.
65-69    0.183  0.1608482  0.002751  0.000081  0.03193   0.15954   71943.    935.   330189.
70-74    0.183  0.1608482  0.003821  0.000112  0.04814   0.22923   60465.   1047.   266172.
75-79    0.183  0.1608482  0.003850  0.000113  0.07570   0.32855   46605.    762.   192209.
80-84    0.183  0.1608482  0.003948  0.000116  0.11794   0.45666   31293.    476.   117128.
85-99    0.183  0.1608482  0.002197  0.000064  0.21587   1.00000   17003.    176.    77946.

TOTALS                                                                    5492.  5611034.

EXCESS DEATHS        150.   (  2.81%)
LIFE EXPECTANCY LOST    0.0204 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 4.84

EXCESS DEATHS        727.   ( 13.62%)
LIFE EXPECTANCY LOST    0.0985 YEARS
```

TABLE L.31

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	1.369	0.0201000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	2.281	0.0201000	0.000001	0.000000	0.00206	0.01028	99165.	1.	493272.
25-29	3.194	0.0201000	0.000003	0.000000	0.00151	0.00755	98145.	2.	488875.
30-34	4.106	0.0201000	0.000007	0.000001	0.00158	0.00791	97405.	4.	485095.
35-39	5.019	0.0201000	0.000047	0.000005	0.00228	0.01162	96634.	25.	480360.
40-44	5.931	0.0201000	0.000165	0.000020	0.00339	0.01772	95512.	87.	473314.
45-49	6.844	0.0201000	0.000371	0.000051	0.00534	0.02865	93819.	195.	462344.
50-54	7.756	0.0201000	0.000828	0.000129	0.00834	0.04545	91131.	426.	445223.
55-59	8.669	0.0201000	0.001322	0.000230	0.01369	0.07338	86990.	650.	418788.
60-64	9.581	0.0201000	0.002142	0.000422	0.02084	0.11066	80607.	994.	380248.
65-69	10.494	0.0201000	0.002751	0.000580	0.03193	0.16164	71687.	1095.	328616.
70-74	11.406	0.0201000	0.003821	0.000876	0.04814	0.23217	60100.	1240.	264081.
75-79	12.319	0.0201000	0.003850	0.000953	0.07570	0.33136	46146.	912.	189946.
80-84	13.231	0.0201000	0.003948	0.001050	0.11794	0.45919	30855.	576.	115248.
85-99	14.144	0.0201000	0.002197	0.000625	0.21587	1.00000	16687.	215.	76302.
TOTALS								6422.	5599664.

EXCESS DEATHS 1080. (20.22%)
LIFE EXPECTANCY LOST 0.1341 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS 1782. (33.37%)
LIFE EXPECTANCY LOST 0.2212 YEARS

TABLE L.3m

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.168	10.6070300	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	0.179	4.4721920	0.000001	0.000001	0.00206	0.01028	99165.	1.	493270.
25-29	0.181	2.4482230	0.000003	0.000001	0.00151	0.00755	98145.	2.	488872.
30-34	0.182	1.4328200	0.000007	0.000002	0.00158	0.00792	97404.	4.	485089.
35-39	0.182	0.9060763	0.000047	0.000008	0.00228	0.01163	96632.	26.	480348.
40-44	0.182	0.6069744	0.000165	0.000018	0.00339	0.01771	95508.	87.	473301.
45-49	0.182	0.4251776	0.000371	0.000029	0.00539	0.02854	93817.	185.	462358.
50-54	0.183	0.3086347	0.000828	0.000047	0.00834	0.04505	91139.	390.	445353.
55-59	0.183	0.2306778	0.001322	0.000056	0.01364	0.07257	87033.	577.	419178.
60-64	0.183	0.1766511	0.002192	0.000071	0.02084	0.10909	80717.	862.	381148.
65-69	0.183	0.1380863	0.002751	0.000069	0.03193	0.15949	71912.	931.	330054.
70-74	0.183	0.1098581	0.003821	0.000077	0.04814	0.22909	60442.	1037.	266094.
75-79	0.183	0.0887442	0.003850	0.000062	0.07570	0.32838	46595.	752.	192193.
80-84	0.183	0.0726516	0.003948	0.000052	0.11794	0.45649	31294.	469.	117151.
85-99	0.183	0.0601817	0.002147	0.000024	0.21587	1.00000	17009.	173.	77990.
TOTALS								5496.	5610300.

EXCESS DEATHS 154. (2.89%)
LIFE EXPECTANCY LOST 0.0277 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 4.84

EXCESS DEATHS 747. (13.99%)
LIFE EXPECTANCY LOST 0.1341 YEARS

TABLE L.3n

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	10.000	0.0000168	0.000000	0.000168	0.00168	0.00919	100000.	84.	497700.
20-24	30.000	0.0000168	0.000001	0.000505	0.00206	0.01277	99081.	249.	492236.
25-29	50.000	0.0000168	0.000003	0.000841	0.00151	0.01171	97816.	410.	486209.
30-34	70.000	0.0000168	0.000007	0.001177	0.00158	0.01373	96670.	569.	480027.
35-39	90.000	0.0000168	0.000047	0.001514	0.00228	0.01905	95343.	737.	472161.
40-44	110.000	0.0000168	0.000165	0.001850	0.00339	0.02667	93527.	930.	461371.
45-49	130.000	0.0000168	0.000371	0.002187	0.00539	0.03896	91033.	1141.	446237.
50-54	150.000	0.0000168	0.000828	0.002523	0.00834	0.05680	87486.	1424.	424883.
55-59	170.000	0.0000168	0.001322	0.002859	0.01369	0.08548	82516.	1650.	394684.
60-64	190.000	0.0000168	0.002192	0.003196	0.02084	0.12290	75463.	1905.	353619.
65-69	200.000	0.0000168	0.002751	0.003364	0.03193	0.17323	66188.	1843.	301367.
70-74	200.000	0.0000168	0.003821	0.003364	0.04814	0.24166	54722.	1717.	239028.
75-79	200.000	0.0000168	0.003850	0.003364	0.07570	0.33938	41498.	1225.	169856.
80-84	200.000	0.0000168	0.003948	0.003364	0.11794	0.46541	27415.	745.	101868.
85-99	200.000	0.0000168	0.002197	0.003364	0.21587	1.00000	14656.	368.	66185.
TOTALS								14447.	5387424.

EXCESS DEATHS 9655. (180.74%)
LIFE EXPECTANCY LOST 2.2565 YEARS

TABLE 1.30

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OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

                                  DEATH RATES              PROBABILITY  ALIVE    LUNG    PERSON
 AGE    TOTAL    RISK                                           OF        AT    CANCER   -YEARS
GROUP   DOSE     INDEX          LUNG CANCER        OTHER      DYING     START   DEATHS
                           NATURAL    EXCESS

15-19   0.000  0.0000168  0.000000  0.000000  0.00168   0.00835  100000.      0.   497908.
20-24  10.000  0.0000168  0.000001  0.000168  0.00206   0.01111   99165.     83.   493065.
25-29  30.000  0.0000168  0.000003  0.000505  0.00151   0.01005   98063.    248.   487848.
30-34  50.000  0.0000168  0.000007  0.000841  0.00158   0.01207   97078.    409.   482452.
35-39  70.000  0.0000168  0.000047  0.001177  0.00228   0.01734   95906.    582.   475346.
40-44  80.000  0.0000168  0.000165  0.001346  0.00339   0.02421   94237.    703.   465461.
45-49  80.000  0.0000168  0.000371  0.001346  0.00539   0.03491   91956.    775.   451706.
50-54  80.000  0.0000168  0.000828  0.001346  0.00834   0.05123   88745.    940.   432260.
55-59  80.000  0.0000168  0.001322  0.001346  0.01369   0.07853   84199.   1078.   404236.
60-64  80.000  0.0000168  0.002192  0.001346  0.02084   0.11475   77586.   1242.   305221.
65-69  80.000  0.0000168  0.002751  0.001346  0.03143   0.16484   68683.   1287.   314261.
70-74  70.000  0.0000168  0.003821  0.001177  0.04814   0.23332   57361.   1259.   251866.
75-79  50.000  0.0000168  0.003850  0.000841  0.07570   0.33049   43977.    849.   181065.
80-84  30.000  0.0000168  0.003948  0.000505  0.11794   0.45771   29421.    490.   110028.
85-99  10.000  0.0000168  0.002197  0.000168  0.21587   1.00000   15555.    173.    73108.

TOTALS                                                                     10169.  5485824.

 EXCESS DEATHS     4827.   ( 90.36%)
 LIFE EXPECTANCY LOST    1.2725 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

 EXCESS DEATHS     6372.   (119.28%)
 LIFE EXPECTANCY LOST    1.6796 YEARS
```

TABLE L.3p

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.044	0.0001491	0.000000	0.000007	0.00168	0.00839	100000.	3.	497901.
20-24	1.184	0.0000838	0.000001	0.000099	0.00206	0.01077	99161.	49.	493133.
25-29	2.918	0.0000716	0.000003	0.000209	0.00151	0.00858	98094.	103.	488363.
30-34	3.686	0.0000687	0.000007	0.000253	0.00158	0.00916	97252.	126.	484029.
35-39	3.914	0.0000680	0.000047	0.000266	0.00228	0.01291	96360.	150.	478686.
40-44	3.976	0.0000678	0.000165	0.000270	0.00339	0.01895	95117.	205.	471064.
45-49	3.993	0.0000678	0.000371	0.000271	0.00539	0.02971	93315.	295.	459607.
50-54	3.998	0.0000677	0.000828	0.000271	0.00834	0.04612	90542.	486.	442187.
55-59	3.999	0.0000677	0.001322	0.000271	0.01369	0.07357	86366.	662.	415743.
60-64	3.999	0.0000677	0.002192	0.000271	0.02084	0.10998	80012.	930.	377634.
65-69	3.956	0.0000679	0.002751	0.000268	0.03193	0.16033	71212.	986.	326686.
70-74	2.815	0.0000720	0.003821	0.000203	0.04814	0.22458	59795.	1059.	263164.
75-79	1.081	0.0000851	0.003850	0.000092	0.07570	0.32848	46067.	749.	190001.
80-84	0.313	0.0001057	0.003948	0.000033	0.11794	0.45643	30935.	461.	115811.
85-99	0.085	0.0001326	0.002197	0.000011	0.21587	1.00000	16815.	170.	77106.
TOTALS								6435.	5581110.

EXCESS DEATHS 1093. (20.47%)
LIFE EXPECTANCY LOST 0.3196 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 6.74

EXCESS DEATHS 7369. (137.95%)
LIFE EXPECTANCY LOST 2.1541 YEARS

TABLE L.39

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.000	0.0000168	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	0.000	0.0000168	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	10.000	0.0000168	0.000003	0.000168	0.00151	0.00838	98145.	84.	488669.
30-34	30.000	0.0000168	0.000007	0.000505	0.00158	0.01041	97323.	248.	484078.
35-39	50.000	0.0000168	0.000047	0.000841	0.00228	0.01574	96310.	424.	477751.
40-44	70.000	0.0000168	0.000165	0.001177	0.00339	0.02339	94794.	629.	468405.
45-49	90.000	0.0000168	0.000371	0.001514	0.00539	0.03573	92577.	857.	454565.
50-54	110.000	0.0000168	0.000828	0.001850	0.00834	0.05362	89269.	1163.	434269.
55-59	130.000	0.0000168	0.001322	0.002187	0.01369	0.08240	84482.	1420.	404758.
60-64	150.000	0.0000168	0.002192	0.002523	0.02084	0.11995	77521.	1716.	363863.
65-69	170.000	0.0000168	0.002751	0.002859	0.03193	0.17114	68222.	1745.	311010.
70-74	190.000	0.0000168	0.003821	0.003196	0.04814	0.24102	56547.	1734.	247098.
75-79	200.000	0.0000168	0.003850	0.003364	0.07570	0.33938	47918.	1267.	175667.
80-84	200.000	0.0000168	0.003968	0.003364	0.11794	0.46541	28353.	770.	105353.
85-99	200.000	0.0000168	0.002197	0.003364	0.21587	1.00000	15157.	381.	68450.
TOTALS								12437.	5475109.

EXCESS DEATHS : 7095. (132.82%)
LIFE EXPECTANCY LOST 1.3796 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS 11707. (219.16%)
LIFE EXPECTANCY LOST 2.2764 YEARS

TABLE L.5.

```
OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING  WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

  AGE    TOTAL      RISK              DEATH RATES             PROBABILITY   ALIVE    LUNG     PERSON
 GROUP   DOSE       INDEX          LUNG CANCER        OTHER       OF          AT     CANCER   -YEARS
                               NATURAL     EXCESS                DYING      START.   DEATHS

 15-19  10.000  0.0000000  0.000000  0.000000  0.00168  0.00835  100000.      0.   497908.
 20-24  30.000  0.0000000  0.000001  0.000000  0.00206  0.01028   99165.      0.   493272.
 25-29  50.000  0.0000000  0.000003  0.000000  0.00151  0.00755   98145.      1.   488876.
 30-34  70.000  0.0000000  0.000007  0.000000  0.00158  0.00791   97405.      3.   485096.
 35-39  90.000  0.0000100  0.000047  0.000900  0.00228  0.01603   96634.    454.   479289.
 40-44 110.000  0.0000100  0.000165  0.001100  0.00339  0.02301   95085.    594.   469936.
 45-49 130.000  0.0000100  0.000371  0.001300  0.00534  0.03469   92897.    763.   456382.
 50-54 150.000  0.0000200  0.000828  0.003000  0.00834  0.05905   89674.   1665.   434999.
 55-59 170.000  0.0000200  0.001322  0.003400  0.01369  0.08745   84379.   1903.   403057.
 60-64 190.000  0.0000200  0.002192  0.003800  0.02084  0.12555   76958.   2158.   360094.
 65-69 200.000  0.0000500  0.002751  0.010000  0.03193  0.20021   67296.   3845.   301543.
 70-74 200.000  0.0000500  0.003821  0.010000  0.04814  0.26641   53823.   3198.   231417.
 75-79 200.000  0.0000500  0.003850  0.010000  0.07570  0.36094   39484.   2204.   159141.
 80-84 200.000  0.0000500  0.003948  0.010000  0.11794  0.48286   25233.   1289.    92380.
 85-99 200.000  0.0000500  0.002197  0.010000  0.21587  1.00000   13049.    698.    57215.

 TOTALS                                                                  18776.  5410595.

 EXCESS DEATHS  13434.   (251.48%)
 LIFE EXPECTANCY LOST    2.0247 YEARS
```

TABLE L.3a

```
OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING  WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

 AGE    TOTAL     RISK              DEATH RATES                  PROBABILITY  ALIVE    LUNG     PERSON
GROUP   DOSE      INDEX          LUNG CANCER          OTHER           OF        AT     CANCER   -YEARS
                            NATURAL      EXCESS                     DYING     START   DEATHS

15-19   0.000  0.0000000  0.000000   0.000000    0.00168     0.00835  100000.       0.    497908.
20-24  10.000  0.0000000  0.000001   0.000000    0.00206     0.01028   99165.       0.    493272.
25-29  30.000  0.0000000  0.000003   0.000000    0.00151     0.00755   98145.       1.    488876.
30-34  50.000  0.0000000  0.000007   0.000000    0.00158     0.00791   97405.       3.    485096.
35-39  70.000  0.0000100  0.000047   0.000700    0.00228     0.01505   96634.     358.    479529.
40-44  80.000  0.0000100  0.000165   0.000800    0.00339     0.02154   95180.     454.    470758.
45-49  80.000  0.0000100  0.000371   0.000800    0.00539     0.03228   93130.     536.    458093.
50-54  80.000  0.0000200  0.000828   0.001600    0.00834     0.05244   90124.    1065.    438697.
55-59  80.000  0.0000200  0.001322   0.001600    0.01369     0.07970   85398.    1147.    409736.
60-64  80.000  0.0000200  0.002192   0.001600    0.02084     0.11588   78591.    1402.    369720.
65-69  80.000  0.0000500  0.002751   0.004000    0.03193     0.17585   69484.    2133.    315889.
70-74  70.000  0.0000500  0.003821   0.003500    0.04814     0.24218   57265.    1831.    250054.
75-79  50.000  0.0000500  0.003850   0.002500    0.07570     0.33652   43397.    1130.    177986.
80-84  30.000  0.0000500  0.003948   0.001500    0.11794     0.46041   28793.     585.    107438.
85-99  10.000  0.0000500  0.002147   0.000500    0.21587     1.00000   15537.     192.     71084.

TOTALS                                                                         10889.   5514127.

EXCESS DEATHS     5547.   (103.84%)
LIFE EXPECTANCY LOST     0.9894 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

EXCESS DEATHS     7322.   (137.07%)
LIFE EXPECTANCY LOST     1.3060 YEARS
```

TABLE L.3c

```
OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING  WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

                                       DEATH RATES              PROBABILITY  ALIVE     LUNG      PERSON
  AGE     TOTAL     RISK                LUNG CANCER       OTHER      OF        AT      CANCER     YEARS
 GROUP    DOSE      INDEX          NATURAL     EXCESS              DYING     START     DEATHS

 15-19    0.044   0.0000055   0.000000   0.000000   0.00168   0.00836   100000.        0.    497908.
 20-24    1.184   0.0000074   0.000001   0.000009   0.00206   0.01032    99164.        5.    493261.
 25-29    2.918   0.0000124   0.000003   0.000036   0.00151   0.00773    98141.       19.    488808.
 30-34    3.686   0.0000208   0.000007   0.000077   0.00158   0.00829    97383.       41.    484895.
 35-39    3.914   0.0000333   0.000047   0.000130   0.00228   0.01224    96575.       85.    479918.
 40-44    3.976   0.0000505   0.000165   0.000201   0.00339   0.01861    95394.      173.    472518.
 45-49    3.993   0.0000732   0.000371   0.000292   0.00539   0.02982    93619.      306.    461079.
 50-54    3.998   0.0001029   0.000828   0.000409   0.00834   0.04678    90827.      549.    443428.
 55-59    3.999   0.0001387   0.001322   0.000555   0.01369   0.07488    86578.      782.    416472.
 60-64    3.999   0.0001834   0.002192   0.000733   0.02084   0.11204    80095.     1105.    377596.
 65-69    3.956   0.0002377   0.002751   0.000440   0.03193   0.16315    71121.     1202.    325737.
 70-74    2.815   0.0003194   0.003821   0.000899   0.04814   0.23226    59518.     1234.    261511.
 75-79    1.081   0.0004682   0.003850   0.000506   0.07570   0.32987    45695.      820.    188282.
 80-84    0.313   0.0007093   0.003948   0.000222   0.11794   0.45695    30621.      478.    114588.
 85-99    0.085   0.0010725   0.002197   0.000091   0.21587   1.00000    16629.      174.     76224.

 TOTALS                                                                           6972.   5582219.

 EXCESS DEATHS      1630.    ( 30.52%)
 LIFE EXPECTANCY LOST    0.3085 YEARS

 ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 6.74

 EXCESS DEATHS   10988.    (205.70%)
 LIFE EXPECTANCY LOST    2.0794 YEARS
```

TABLE L.30

```
OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

  AGE    TOTAL     RISK              DEATH RATES                  PROBABILITY  ALIVE    LUNG      PERSON
 GROUP   DOSE      INDEX        LUNG CANCER              OTHER       OF         AT     CANCER    -YEARS
                              NATURAL      EXCESS                   DYING      START   DEATHS

 15-19    0.000  0.0000000  0.000000   0.000000    0.00168    0.00835   100000.       0.    497908.
 20-24    0.000  0.0000000  0.000001   0.000000    0.00206    0.01028    99165.       0.    493272.
 25-29   10.000  0.0000000  0.000003   0.000000    0.00151    0.00755    98145.       1.    488876.
 30-34   30.000  0.0000000  0.000007   0.000000    0.00158    0.00791    97405.       3.    485096.
 35-39   50.000  0.0000100  0.000047   0.000500    0.00228    0.01406    96634.     262.    479768.
 40-44   70.000  0.0000100  0.000165   0.000700    0.00339    0.02106    95276.     408.    471346.
 45-49   90.000  0.0000100  0.000371   0.000900    0.00539    0.03276    93270.     583.    458666.
 50-54  110.000  0.0000200  0.000828   0.002200    0.00834    0.05528    90214.    1328.    438484.
 55-59  130.000  0.0000200  0.001322   0.002600    0.01369    0.08429    85227.    1600.    407910.
 60-64  150.000  0.0000200  0.002197   0.003000    0.02084    0.12205    78043.    1900.    365886.
 65-69  170.000  0.0000500  0.002751   0.008500    0.03193    0.19419    68518.    3467.    308130.
 70-74  190.000  0.0000500  0.003821   0.009500    0.04814    0.26457    55213.    3166.    237676.
 75-79  200.000  0.0000500  0.003850   0.010000    0.07570    0.36094    40605.    2267.    163660.
 80-84  200.000  0.0000500  0.003948   0.010000    0.11794    0.48286    25949.    1325.     95005.
 85-99  200.000  0.0000500  0.002197   0.010000    0.21587    1.00000    13419.     718.     58839.

TOTALS                                                                          17028.   5450515.

EXCESS DEATHS    11686.    (218.76%)
LIFE EXPECTANCY LOST     1.6256 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS    19282.    (360.95%)
LIFE EXPECTANCY LOST     2.6822 YEARS
```

TABLE L.3V

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	10.000	0.0201000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	30.000	0.0201000	0.000001	0.000001	0.00206	0.01028	99165.	1.	493271.
25-29	50.000	0.0201000	0.000003	0.000003	0.00151	0.00756	98145.	3.	488870.
30-34	70.000	0.0201000	0.000007	0.000010	0.00158	0.00796	97403.	8.	485077.
35-39	90.000	0.0201000	0.000047	0.000085	0.00228	0.01201	96628.	63.	480235.
40-44	110.000	0.0201000	0.000165	0.000365	0.00339	0.01941	95467.	250.	472687.
45-49	130.000	0.0201000	0.000371	0.000969	0.00534	0.03310	93614.	617.	460279.
50-54	150.000	0.0201000	0.000828	0.002496	0.00834	0.05668	90515.	1462.	439626.
55-59	170.000	0.0201000	0.001322	0.004517	0.01369	0.09303	85385.	2375.	406744.
60-64	190.000	0.0201000	0.002192	0.008371	0.02084	0.14531	77442.	3785.	358340.
65-69	200.000	0.0201000	0.002751	0.011059	0.03193	0.20443	66189.	4085.	295827.
70-74	200.000	0.0201000	0.003821	0.015360	0.04814	0.28581	52657.	4288.	223555.
75-79	200.000	0.0201000	0.003850	0.015477	0.07570	0.37820	37607.	2893.	149674.
80-84	200.000	0.0201000	0.003948	0.015871	0.11794	0.49782	23384.	1675.	84504.
85-99	200.000	0.0201000	0.002197	0.008832	0.21587	1.00000	11743.	571.	51755.
TOTALS								22076.	5388345.

EXCESS DEATHS 16734. (313.26%)
LIFE EXPECTANCY LOST 2.2472 YEARS

TABLE L.3w

```
OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED OVER WINDOW FROM 5 TO 25 YEARS AFTER EACH INCREMENT

 AGE     TOTAL     RISK              DEATH RATES              PROBABILITY  ALIVE    LUNG     PERSON
GROUP    DOSE      INDEX          LUNG CANCER        OTHER        OF        AT     CANCER   -YEARS
                              NATURAL    EXCESS                  DYING     START   DEATHS

15-19    0.000   0.0201000   0.000000   0.000000    0.00168    0.00835   100000.      0.    497908.
20-24   10.000   0.0201000   0.000001   0.000000    0.00206    0.01028    99165.      1.    493272.
25-29   30.000   0.0201000   0.000003   0.000002    0.00151    0.00756    98145.      2.    488871.
30-34   50.000   0.0201000   0.000007   0.000007    0.00158    0.00794    97404.      7.    485085.
35-39   70.000   0.0201000   0.000047   0.000066    0.00228    0.01192    96630.     54.    480266.
40-44   80.000   0.0201000   0.000165   0.000265    0.00339    0.01893    95478.    203.    472860.
45-49   80.000   0.0201000   0.000371   0.000597    0.00539    0.03129    93671.    446.    460990.
50-54   80.000   0.0201000   0.000828   0.001331    0.00834    0.05117    90740.    954.    441991.
55-59   80.000   0.0201000   0.001322   0.002126    0.01369    0.08212    86097.   1422.    412557.
60-64   80.000   0.0201000   0.002192   0.003525    0.02084    0.12435    79027.   2115.    370024.
65-69   80.000   0.0201000   0.002751   0.004424    0.03143    0.17760    69200.   2255.    314276.
70-74   70.000   0.0201000   0.003821   0.005376    0.04814    0.24925    56910.   2275.    247398.
75-79   50.000   0.0201000   0.003850   0.003869    0.07570    0.34104    42725.   1348.    174674.
80-84   30.000   0.0201000   0.003948   0.002381    0.11794    0.46278    28154.    664.    104847.
85-99   10.000   0.0201000   0.002197   0.000442    0.21587    1.00000    15125.    183.     69220.

TOTALS                                                                          11930.   5514229.

EXCESS DEATHS     6588.   (123.33%)
LIFE EXPECTANCY LOST    0.9884 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.32

EXCESS DEATHS     8697.   (162.80%)
LIFE EXPECTANCY LOST    1.3047 YEARS
```

TABLE L.3x

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES* LUNG CANCER NATURAL		OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
				EXCESS					
15-19	0.044	0.1927564	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	1.184	0.1269842	0.000001	0.000000	0.00206	0.01028	99165.	1.	493270.
25-29	2.918	0.1133061	0.000003	0.000001	0.00151	0.00755	98145.	2.	488872.
30-34	3.686	0.1100073	0.000007	0.000003	0.00158	0.00792	97404.	5.	485089.
35-39	3.914	0.1091760	0.000047	0.000020	0.00228	0.01169	96632.	32.	480333.
40-44	3.976	0.1089607	0.000165	0.000071	0.00339	0.01797	95503.	112.	473209.
45-49	3.993	0.1089027	0.000371	0.000161	0.00534	0.02918	93786.	246.	462054.
50-54	3.998	0.1088861	0.000828	0.000360	0.00834	0.04655	91049.	528.	444566.
55-59	3.999	0.1088820	0.001322	0.000576	0.01369	0.07498	86811.	792.	417570.
60-64	3.999	0.1088806	0.002192	0.000954	0.02084	0.11302	80302.	1191.	378367.
65-69	3.956	0.1090316	0.002751	0.001186	0.03193	0.16418	71226.	1284.	326023.
70-74	2.815	0.1138209	0.003821	0.001224	0.04814	0.23350	59533.	1319.	261371.
75-79	1.081	0.1284560	0.003850	0.000535	0.07570	0.32996	45631.	824.	188010.
80-84	0.313	0.1502339	0.003948	0.000186	0.11794	0.45685	30575.	473.	114423.
85-99	0.085	0.1771057	0.002197	0.000033	0.21587	1.00000	16607.	170.	76142.
TOTALS								6978.	5587202.

EXCESS DEATHS 1636. (30.63%)
LIFE EXPECTANCY LOST 0.2587 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 4.84

EXCESS DEATHS 7919. (148.24%)
LIFE EXPECTANCY LOST 1.2520 YEARS

TABLE L.3y

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM 10 YEARS AFTER EACH INCREMENT

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.000	0.0201000	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	0.000	0.0201000	0.000001	0.000000	0.00206	0.01028	99165.	0.	493272.
25-29	10.000	0.0201000	0.000003	0.000001	0.00151	0.00755	98145.	2.	488874.
30-34	30.000	0.0201000	0.000007	0.000004	0.00158	0.00793	97404.	5.	485089.
35-39	50.000	0.0201000	0.000047	0.000047	0.00228	0.01183	96632.	45.	480299.
40-44	70.000	0.0201000	0.000165	0.000232	0.00339	0.01876	95489.	188.	472953.
45-49	90.000	0.0201000	0.000371	0.000671	0.00539	0.03165	93698.	480.	461034.
50-54	110.000	0.0201000	0.000828	0.001831	0.00834	0.05353	90732.	1174.	441405.
55-59	130.000	0.0201000	0.001322	0.003454	0.01369	0.08820	85875.	1959.	410146.
60-64	150.000	0.0201000	0.002142	0.006609	0.02084	0.13775	78301.	3202.	363873.
65-69	170.000	0.0201000	0.002751	0.009400	0.03193	0.19781	67515.	3681.	302962.
70-74	190.000	0.0201000	0.003821	0.014592	0.04814	0.28306	54160.	4242.	230352.
75-79	200.000	0.0201000	0.003850	0.015477	0.07570	0.37820	38829.	2987.	154538.
80-84	200.000	0.0201000	0.003948	0.015871	0.14794	0.49782	24144.	1729.	87250.
85-99	200.000	0.0201000	0.002197	0.008832	0.21587	1.00000	12125.	589.	55437.
TOTALS								20284.	5423385.

EXCESS DEATHS 14942. (279.72%)
LIFE EXPECTANCY LOST 1.8968 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 1.65

EXCESS DEATHS 24655. (461.53%)
LIFE EXPECTANCY LOST 3.1298 YEARS

TABLE L.3z

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE VARYING WITH AGE
EXPOSURE ACCUMULATED USING 10YR MEDIAN LOGNORMAL LATENT PERIOD DISTRIBUTION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
15-19	0.044	15.0696500	0.000000	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	1.184	2.8563020	0.000001	0.000003	0.00206	0.01029	99165.	2.	493268.
25-29	2.918	1.1886150	0.000003	0.000010	0.00151	0.00760	98144.	7.	488854.
30-34	3.686	0.6553189	0.000007	0.000017	0.00158	0.00799	97398.	12.	485041.
35-39	3.914	0.4081146	0.000047	0.000075	0.00228	0.01196	96619.	59.	480203.
40-44	3.976	0.2724064	0.000165	0.000179	0.00339	0.01850	95464.	163.	472889.
45-49	3.993	0.1905428	0.000371	0.000282	0.00534	0.02977	93697.	301.	461479.
50-54	3.998	0.1382783	0.000828	0.000458	0.00834	0.04701	90908.	571.	443770.
55-59	3.999	0.1033430	0.001322	0.000546	0.01369	0.07484	86634.	779.	416751.
60-64	3.999	0.0791371	0.002142	0.000694	0.02084	0.11186	80150.	1090.	377893.
65-69	3.956	0.0620373	0.002751	0.000675	0.03193	0.16204	71184.	1118.	326236.
70-74	2.815	0.0539205	0.003821	0.000580	0.04814	0.23103	59650.	1154.	262290.
75-79	1.081	0.0558684	0.003850	0.000233	0.07570	0.32895	45869.	772.	189122.
80-84	0.313	0.0631296	0.003948	0.000078	0.11794	0.45656	30780.	464.	115220.
85-99	0.085	0.0733696	0.002197	0.000014	0.21587	1.00000	16727.	170.	76703.
TOTALS								6660.	5587619.

EXCESS DEATHS 1318. (24.68%)
LIFE EXPECTANCY LOST 0.2545 YEARS

ADJUSTED FOR COMPARABILITY WITH TOTAL-PERIOD INDEX BY FACTOR 4.84

EXCESS DEATHS 6380. (119.43%)
LIFE EXPECTANCY LOST 1.2318 YEARS

TABLE L.4

OCCUPATIONAL ACCIDENTS IN A PRESUMABLY "SAFE" INDUSTRY
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON-YEARS
15-19	1.000	0.0001000	0.000000	0.000100	0.00168	0.00885	100000.	50.	497786.
20-24	1.000	0.0001000	0.000001	0.000100	0.00206	0.01077	99115.	50.	492901.
25-29	1.000	0.0001000	0.000003	0.000100	0.00151	0.00804	98047.	50.	488264.
30-34	1.000	0.0001000	0.000007	0.000100	0.00158	0.00840	97259.	52.	484248.
35-39	1.000	0.0001000	0.000047	0.000100	0.00228	0.01209	96441.	70.	479287.
40-44	1.000	0.0001000	0.000165	0.000100	0.00339	0.01811	95276.	125.	472051.
45-49	1.000	0.0001000	0.000371	0.000100	0.00539	0.02888	93550.	217.	460961.
50-54	1.000	0.0001000	0.000828	0.000100	0.00834	0.04531	90848.	412.	443868.
55-59	1.000	0.0001000	0.001322	0.000100	0.01369	0.07278	86732.	594.	417679.
60-64	1.000	0.0001000	0.002192	0.000100	0.02084	0.10922	80420.	870.	379715.
65-69	0.000	0.0001000	0.002751	0.000000	0.03193	0.15920	71636.	905.	328844.
70-74	0.000	0.0001000	0.003821	0.000000	0.04814	0.22880	60231.	1013.	265214.
75-79	0.000	0.0001000	0.003850	0.000000	0.07570	0.32817	46450.	738.	191623.
80-84	0.000	0.0001000	0.003948	0.000000	0.11794	0.45634	31207.	461.	116837.
85-99	0.000	0.0001000	0.002197	0.000000	0.21587	1.00000	16966.	171.	77801.
TOTALS								5778.	5597072.

EXCESS DEATHS 436. (8.17%)
LIFE EXPECTANCY LOST 0.1600 YEARS

TABLE L.5

OCCUPATIONAL EXPOSURE TO 5 F/ML FROM AGE 15 to 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT

AGE GROUP	TOTAL DOSE	RISK COGFF	DEATH RATES LUNG CAN	DEATH RATES OTHER	PROB OF DYING	ALIVE AT START	LUNG CAN DEATHS	PERSON - YEARS
15-19	12.500	0.462F-03	0.000000	0.00168	0.00835	100000.	0.	497908.
20-24	37.500	0.462F-03	0.000001	0.00206	0.01028	99165.	1.	493270.
25-29	62.500	0.462F-03	0.000003	0.00151	0.00755	98145.	2.	488875.
30-34	87.500	0.462F-03	0.000007	0.00158	0.00791	97405.	4.	485097.
35-39	112.500	0.462F-03	0.000049	0.00228	0.01160	96634.	24.	480362.
40-44	137.500	0.462F-03	0.000175	0.00339	0.01767	95513.	83.	473331.
45-49	162.500	0.462F-03	0.000399	0.00539	0.02853	93825.	84.	452398.
50-54	187.500	0.462F-03	0.000900	0.00834	0.04517	91147.	401.	445364.
55-59	212.500	0.462F-03	0.001452	0.01369	0.07291	87030.	608.	419085.
60-64	237.500	0.462F-03	0.002433	0.02084	0.10985	80684.	926.	380834.
65-69	250.000	0.462F-03	0.003069	0.03193	0.16054	71821.	1011.	329441.
70-74	250.000	0.462F-03	0.004262	0.04814	0.23050	60291.	1130.	265198.
75-79	250.000	0.462F-03	0.004295	0.07570	0.32966	46394.	821.	191193.
80-84	250.000	0.462F-03	0.004404	0.11794	0.45758	31100.	512.	116317.
85-99	250.000	0.462F-03	0.002451	0.21587	0.00000	16869.	189.	77267.
TOTALS							5896	5605935

EXCESS DEATHS 554. (10.38%)
LIFE EXPECTANCY LOST 0.0713 YEARS

TABLE L.4

TABLE L.6

GENERAL POPULATION

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	0.000	0.0000000	0.000000	0.000000	0.00168	0.00835	60000.	0.	298745.
20-24	0.000	0.0000000	0.000001	-0.000001	0.00206	0.01027	59499.	0.	295963.
25-29	0.000	0.0000000	0.000003	-0.000003	0.00151	0.00753	58887.	0.	293327.
30-34	0.000	0.0000000	0.000007	-0.000006	0.00158	0.00788	58444.	0.	291066.
35-39	0.000	0.0000000	0.000047	-0.000039	0.00228	0.01140	57983.	2.	288262.
40-44	0.000	0.0000000	0.000165	-0.000138	0.00334	0.01694	57322.	8.	284178.
45-49	0.000	0.0000000	0.000371	-0.000311	0.00539	0.02684	56351.	17.	277952.
50-54	0.000	0.0000000	0.000828	-0.000694	0.00834	0.04151	54836.	36.	268451.
55-59	0.000	0.0000000	0.001322	-0.001109	0.01369	0.06715	52560.	54.	253874.
60-64	0.000	0.0000000	0.002192	-0.001838	0.02084	0.10055	49030.	82.	232610.
65-69	0.000	0.0000000	0.002751	-0.002307	0.03193	0.14945	44101.	90.	203582.
70-74	0.000	0.0000000	0.003821	-0.003205	0.04814	0.21634	37510.	103.	166439.
75-79	0.000	0.0000000	0.003850	-0.003229	0.07570	0.31724	29395.	76.	122183.
80-84	0.000	0.0000000	0.003948	-0.003311	0.11794	0.44727	20070.	48.	75703.
85-99	0.000	0.0000000	0.002197	-0.001843	0.21587	1.00000	11093.	18.	51304.
TOTALS								534.	3403631.
SMOKERS									
15-19	0.000	0.0000000	0.000000	0.000000	0.00168	0.00835	40000.	0.	199163.
20-24	0.000	0.0000000	0.000001	0.000001	0.00206	0.01028	39666.	0.	197308.
25-29	0.000	0.0000000	0.000003	0.000004	0.00151	0.00757	39258.	1.	195547.
30-34	0.000	0.0000000	0.000007	0.000009	0.00158	0.00795	38961.	3.	194030.
35-39	0.000	0.0000000	0.000047	0.000059	0.00228	0.01188	38651.	20.	192106.
40-44	0.000	0.0000000	0.000165	0.000208	0.00334	0.01864	38192.	70.	189174.
45-49	0.000	0.0000000	0.000371	0.000467	0.00539	0.03066	37480.	155.	184511.
50-54	0.000	0.0000000	0.000828	0.001042	0.00834	0.04979	36330.	331.	177092.
55-59	0.000	0.0000000	0.001322	0.001663	0.01369	0.07999	34522.	494.	165608.
60-64	0.000	0.0000000	0.002192	0.002758	0.02084	0.12098	31760.	737.	148988.
65-69	0.000	0.0000000	0.002751	0.003461	0.03193	0.17363	27918.	789.	127085.
70-74	0.000	0.0000000	0.003821	0.004807	0.04814	0.24711	23070.	866.	100426.
75-79	0.000	0.0000000	0.003850	0.004844	0.07570	0.34424	17369.	616.	70850.
80-84	0.000	0.0000000	0.003948	0.004967	0.11794	0.46968	11390.	376.	42172.
85-99	0.000	0.0000000	0.002197	0.002764	0.21587	1.00000	6040.	136.	27353.
TOTALS								4597.	2211407.
NON-SMOKERS AND SMOKERS COMBINED								5131.	5615038.

TABLE L.7a

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT ADDITIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES: LUNG CANCER NATURAL	DEATH RATES: LUNG CANCER EXCESS	DEATH RATES: OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	3.194	0.0000168	0.000000	0.000054	0.00168	0.00862	60000.	16.	298705.
20-24	4.106	0.0000168	0.000001	0.000068	0.00206	0.01061	59483.	20.	295834.
25-29	5.019	0.0000168	0.000003	0.000082	0.00151	0.00795	58851.	23.	293087.
30-34	5.931	0.0000168	0.000007	0.000094	0.00158	0.00837	58383.	29.	290693.
35-39	6.844	0.0000168	0.000047	0.000076	0.00228	0.01147	57894.	35.	287737.
40-44	7.756	0.0000168	0.000165	-0.000008	0.00334	0.01758	57202.	45.	283487.
45-49	8.669	0.0000168	0.000371	-0.000165	0.00534	0.02760	56196.	57.	277084.
50-54	9.581	0.0000168	0.000828	-0.000533	0.00834	0.04228	54645.	79.	267408.
55-59	10.494	0.0000168	0.001322	-0.000432	0.01369	0.06798	52335.	98.	252675.
60-64	11.406	0.0000168	0.002192	-0.001647	0.02084	0.10141	48777.	126.	231299.
65-69	12.319	0.0000168	0.002751	-0.002100	0.03193	0.15033	43831.	132.	202234.
70-74	13.231	0.0000168	0.003821	-0.002482	0.04814	0.21721	37242.	134.	165161.
75-79	14.144	0.0000168	0.003850	-0.002491	0.07570	0.31805	29152.	104.	121107.
80-84	15.056	0.0000168	0.003948	-0.003058	0.11794	0.44747	19881.	67.	74946.
85-99	15.969	0.0000168	0.002147	-0.001574	0.21587	1.00000	10975.	32.	50693.
TOTALS								1003.	3342142.
SMOKERS									
15-19	3.194	0.0000168	0.000000	0.000054	0.00168	0.00862	40000.	11.	199137.
20-24	4.106	0.0000168	0.000001	0.000070	0.00206	0.01062	39655.	14.	197221.
25-29	5.019	0.0000168	0.000003	0.000088	0.00151	0.00798	39234.	18.	195385.
30-34	5.931	0.0000168	0.000007	0.000104	0.00158	0.00845	38921.	22.	193780.
35-39	6.844	0.0000168	0.000047	0.000174	0.00228	0.01245	38592.	42.	191755.
40-44	7.756	0.0000168	0.000165	0.000338	0.00334	0.01928	38111.	95.	188713.
45-49	8.669	0.0000168	0.000371	0.000613	0.00534	0.03137	37376.	181.	183935.
50-54	9.581	0.0000168	0.000828	0.001203	0.00834	0.05056	36204.	358.	176404.
55-59	10.494	0.0000168	0.001322	0.001840	0.01369	0.08081	34374.	521.	164826.
60-64	11.406	0.0000168	0.002192	0.002950	0.02084	0.12182	31596.	762.	148148.
65-69	12.319	0.0000168	0.002751	0.003668	0.03193	0.17448	27747.	810.	126244.
70-74	13.231	0.0000168	0.003821	0.005030	0.04814	0.24795	22405.	882.	99655.
75-79	14.144	0.0000168	0.003850	0.005081	0.07570	0.34502	17226.	627.	70227.
80-84	15.056	0.0000168	0.003948	0.005220	0.11794	0.47035	11283.	383.	41750.
85-99	15.969	0.0000168	0.002147	0.003033	0.21587	1.00000	5976.	141.	27028.
TOTALS								4868.	2204206.
NON-SMOKERS AND SMOKERS COMBINED								5872.	5546348.

TABLE L.4

TABLE L.7b

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT MULTIPLICATIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	3.194	0.0000027	0.000000	0.000009	0.00168	0.00840	60000.	3.	298734.
20-24	4.106	0.0000027	0.000001	0.000010	0.00206	0.01033	59496.	3.	295942.
25-29	5.019	0.0000027	0.000003	0.000011	0.00151	0.00760	58882.	4.	293290.
30-34	5.931	0.0000027	0.000007	0.000010	0.00158	0.00746	58434.	5.	291008.
35-39	6.844	0.0000027	0.000047	-0.000021	0.00228	0.01149	57969.	8.	288178.
40-44	7.756	0.0000027	0.000165	-0.000117	0.00339	0.01705	57303.	14.	284066.
45-49	8.669	0.0000027	0.000371	-0.000288	0.00534	0.02700	56326.	23.	277811.
50-54	9.581	0.0000027	0.000828	-0.000668	0.00834	0.04163	54805.	43.	268282.
55-59	10.494	0.0000027	0.001322	-0.001080	0.01369	0.06724	52524.	61.	253680.
60-64	11.406	0.0000027	0.002192	-0.001808	0.02084	0.10069	48989.	89.	232398.
65-69	12.319	0.0000027	0.002751	-0.002274	0.03193	0.14959	44057.	97.	203364.
70-74	13.231	0.0000027	0.003821	-0.003169	0.04814	0.21648	37467.	108.	166232.
75-79	14.144	0.0000027	0.003850	-0.003191	0.07570	0.31737	29356.	80.	122009.
80-84	15.056	0.0000027	0.003948	-0.003270	0.11744	0.44738	20034.	51.	75580.
85-99	15.969	0.0000027	0.002147	-0.001799	0.21587	1.00000	11074.	20.	51205.
TOTALS								610.	3401777.
SMOKERS									
15-19	3.194	0.0000380	0.000000	0.000121	0.00168	0.00896	40000.	24.	199104.
20-24	4.106	0.0000380	0.000001	0.000157	0.00206	0.01105	39642.	31.	197112.
25-29	5.019	0.0000380	0.000003	0.000194	0.00151	0.00851	39204.	34.	195182.
30-34	5.931	0.0000380	0.000007	0.000234	0.00158	0.00907	38870.	47.	193467.
35-39	6.844	0.0000380	0.000047	0.000319	0.00228	0.01317	38517.	70.	191316.
40-44	7.756	0.0000380	0.000165	0.000502	0.00339	0.02004	38010.	126.	188136.
45-49	8.669	0.0000380	0.000371	0.000796	0.00534	0.03226	37247.	214.	183213.
50-54	9.581	0.0000380	0.000828	0.001406	0.00834	0.05152	36045.	392.	175543.
55-59	10.494	0.0000380	0.001322	0.002062	0.01369	0.08183	34188.	554.	163848.
60-64	11.406	0.0000380	0.002192	0.003191	0.02084	0.12288	31391.	792.	147099.
65-69	12.319	0.0000380	0.002751	0.003929	0.03743	0.17556	27533.	836.	125194.
70-74	13.231	0.0000380	0.003821	0.005310	0.04814	0.24900	22700.	901.	98694.
75-79	14.144	0.0000380	0.003850	0.005381	0.07570	0.34600	17047.	641.	69450.
80-84	15.056	0.0000380	0.003948	0.005539	0.11744	0.47119	11149.	391.	41226.
85-99	15.969	0.0000380	0.002147	0.003370	0.21587	1.00000	5896.	148.	26624.
TOTALS								5206.	2195203.
NON-SMOKERS AND SMOKERS COMBINED								5816.	5596980.

TABLE L.7c

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT ADDITIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	3.194	0.1246200	0.000000	0.000000	0.00168	0.00835	60000.	0.	298745.
20-24	4.106	0.1246200	0.000001	-0.000001	0.00206	0.01027	59499.	0.	295963.
25-29	5.019	0.1246200	0.000003	-0.000002	0.00151	0.00754	58887.	0.	293327.
30-34	5.931	0.1246200	0.000007	-0.000005	0.00158	0.00788	58444.	1.	291066.
35-39	6.844	0.1246200	0.000047	-0.000033	0.00228	0.01143	57983.	4.	288255.
40-44	7.756	0.1246200	0.000165	-0.000113	0.00334	0.01707	57320.	15.	284148.
45-49	8.669	0.1246200	0.000371	-0.000247	0.00534	0.02720	56342.	35.	277861.
50-54	9.581	0.1246200	0.000828	-0.000535	0.00834	0.04227	54804.	79.	268213.
55-59	10.494	0.1246200	0.001322	-0.000830	0.01369	0.06845	52442.	125.	253373.
60-64	11.406	0.1246200	0.002192	-0.001336	0.02084	0.10280	48899.	198.	231701.
65-69	12.319	0.1246200	0.002751	-0.001626	0.03143	0.15234	43872.	227.	202142.
70-74	13.231	0.1246200	0.003821	-0.002189	0.04814	0.22031	37189.	269.	164612.
75-79	14.144	0.1246200	0.003850	-0.002135	0.07570	0.32096	28996.	206.	120214.
80-84	15.056	0.1246200	0.003948	-0.002116	0.11794	0.45056	19689.	136.	74067.
85-99	15.969	0.1246200	0.002197	-0.001137	0.21587	1.00000	10818.	53.	49869.
TOTALS								1347.	3393599.
SMOKERS									
15-19	3.194	0.1246200	0.000000	0.000000	0.00168	0.00835	40000.	0.	199163.
20-24	4.106	0.1246200	0.000001	0.000001	0.00206	0.01028	39666.	0.	197308.
25-29	5.019	0.1246200	0.000003	0.000004	0.00151	0.00757	39258.	1.	195546.
30-34	5.931	0.1246200	0.000007	0.000010	0.00158	0.00796	38961.	3.	194028.
35-39	6.844	0.1246200	0.000047	0.000066	0.00228	0.01192	38651.	22.	192100.
40-44	7.756	0.1246200	0.000165	0.000233	0.00334	0.01877	38190.	75.	189154.
45-49	8.669	0.1246200	0.000371	0.000531	0.00539	0.03048	37474.	166.	184451.
50-54	9.581	0.1246200	0.000828	0.001201	0.00834	0.05055	36313.	359.	176935.
55-59	10.494	0.1246200	0.001322	0.001942	0.01369	0.08128	34477.	539.	165281.
60-64	11.406	0.1246200	0.002192	0.003260	0.02084	0.12314	31675.	809.	148406.
65-69	12.319	0.1246200	0.002751	0.004142	0.03193	0.17644	27773.	870.	126214.
70-74	13.231	0.1246200	0.003821	0.005823	0.04814	0.25043	22873.	958.	99326.
75-79	14.144	0.1246200	0.003850	0.005938	0.07570	0.34782	17133.	682.	69710.
80-84	15.056	0.1246200	0.003948	0.006162	0.11794	0.47284	11174.	417.	41261.
85-99	15.969	0.1246200	0.002197	0.003469	0.21587	1.00000	5890.	151.	26589.
TOTALS								5054.	2205473.
NON-SMOKERS AND SMOKERS COMBINED								6401.	5599072.

TABLE L.4

TABLE L.7d

HOUSEHOLD EXPOSURE TO .01 WL 17 HR/DA FROM BIRTH TO DEATH
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT MULTIPLICATIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	3.194	0.0201000	0.000000	0.000000	0.00168	0.00835	60000.	0.	298745.
20-24	4.106	0.0201000	0.000001	-0.000001	0.00206	0.01097	59499.	0.	295964.
25-29	5.019	0.0201000	0.000003	-0.000002	0.00151	0.00753	58887.	0.	293327.
30-34	5.931	0.0201000	0.000007	-0.000006	0.00158	0.00788	58444.	0.	291068.
35-39	6.844	0.0201000	0.000047	-0.000038	0.00228	0.01140	57983.	2.	288262.
40-44	7.756	0.0201000	0.000165	-0.000134	0.00339	0.01696	57322.	9.	284173.
45-49	8.669	0.0201000	0.000371	-0.000301	0.00539	0.02644	56350.	20.	277937.
50-54	9.581	0.0201000	0.000828	-0.000669	0.00834	0.04163	54832.	43.	268412.
55-59	10.494	0.0201000	0.001322	-0.001064	0.01369	0.06736	52549.	66.	253793.
60-64	11.406	0.0201000	0.002192	-0.001757	0.02084	0.10091	49009.	101.	232463.
65-69	12.319	0.0201000	0.002751	-0.002197	0.03193	0.14991	44064.	113.	203357.
70-74	13.231	0.0201000	0.003821	-0.003041	0.04814	0.21698	37458.	130.	166143.
75-79	14.144	0.0201000	0.003850	-0.003052	0.07570	0.31784	29330.	97.	121863.
80-84	15.056	0.0201000	0.003948	-0.003119	0.11794	0.44780	20008.	63.	75437.
85-99	15.969	0.0201000	0.002197	-0.001729	0.21587	1.00000	11048.	24.	51070.
TOTALS								666.	3402008.
SMOKERS									
15-19	3.194	0.0201000	0.000000	0.000000	0.00168	0.00835	40000.	0.	199163.
20-24	4.106	0.0201000	0.000001	0.000001	0.00206	0.01028	39666.	0.	197308.
25-29	5.019	0.0201000	0.000003	0.000004	0.00151	0.00757	39258.	1.	195546.
30-34	5.931	0.0201000	0.000007	0.000011	0.00158	0.00796	38961.	3.	194028.
35-39	6.844	0.0201000	0.000047	0.000074	0.00228	0.01196	38651.	23.	192096.
40-44	7.756	0.0201000	0.000165	0.000266	0.00334	0.01843	38188.	81.	189130.
45-49	8.669	0.0201000	0.000371	0.000613	0.00539	0.03137	37466.	181.	184375.
50-54	9.581	0.0201000	0.000828	0.001402	0.00834	0.05150	36290.	394.	176738.
55-59	10.494	0.0201000	0.001322	0.002293	0.01369	0.08289	34421.	596.	164871.
60-64	11.406	0.0201000	0.002192	0.003892	0.02084	0.12595	31568.	899.	147678.
65-69	12.319	0.0201000	0.002751	0.004999	0.03193	0.17996	27592.	970.	125137.
70-74	13.231	0.0201000	0.003821	0.007102	0.04814	0.25570	22627.	1070.	97958.
75-79	14.144	0.0201000	0.003850	0.007315	0.07570	0.35230	16841.	763.	68302.
80-84	15.056	0.0201000	0.003948	0.007665	0.11794	0.47679	10908.	466.	40144.
85-99	15.969	0.0201000	0.002197	0.004356	0.21587	1.00000	5707.	168.	25659.
TOTALS								5617.	2148128.
NON-SMOKERS AND SMOKERS COMBINED								6283.	5600136.

TABLE L.7e

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT ADDITIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER: NATURAL	DEATH RATES LUNG CANCER: EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	10.000	0.0000168	0.000000	0.000168	0.00168	0.00919	60000.	50.	298620.
20-24	30.000	0.0000168	0.000001	0.000504	0.00206	0.01277	59449.	149.	295343.
25-29	50.000	0.0000168	0.000003	0.000838	0.00151	0.01170	58690.	245.	291730.
30-34	70.000	0.0000168	0.000007	0.001172	0.00158	0.01370	58003.	339.	288025.
35-39	90.000	0.0000168	0.000047	0.001474	0.00228	0.01885	57208.	431.	283337.
40-44	110.000	0.0000168	0.000165	0.001712	0.00339	0.02600	56130.	520.	276986.
45-49	130.000	0.0000168	0.000371	0.001875	0.00539	0.03747	54671.	602.	268200.
50-54	150.000	0.0000168	0.000828	0.001829	0.00834	0.05352	52622.	680.	256006.
55-59	170.000	0.0000168	0.001322	0.001751	0.01369	0.08040	49806.	734.	238879.
60-64	190.000	0.0000168	0.002192	0.001357	0.02084	0.11480	45802.	765.	215595.
65-69	200.000	0.0000168	0.002751	0.001057	0.03193	0.16363	40543.	707.	185638.
70-74	200.000	0.0000168	0.003821	0.000159	0.04814	0.22941	33904.	594.	149254.
75-79	200.000	0.0000168	0.003850	0.000135	0.07570	0.32862	26130.	429.	107761.
80-84	200.000	0.0000168	0.003948	0.000053	0.11794	0.45644	17543.	263.	65673.
85-99	200.000	0.0000168	0.002197	0.001521	0.21587	1.00000	9535.	161.	43422.
TOTALS								6671.	3264462.
SMOKERS									
15-19	10.000	0.0000168	0.000000	0.000168	0.00168	0.00919	40000.	33.	199080.
20-24	30.000	0.0000168	0.000001	0.000506	0.00206	0.01278	39632.	100.	196894.
25-29	50.000	0.0000168	0.000003	0.000845	0.00151	0.01173	39126.	165.	194481.
30-34	70.000	0.0000168	0.000007	0.001186	0.00158	0.01378	38667.	224.	192001.
35-39	90.000	0.0000168	0.000047	0.001573	0.00228	0.01934	38134.	306.	188823.
40-44	110.000	0.0000168	0.000165	0.002058	0.00339	0.02768	37397.	410.	184386.
45-49	130.000	0.0000168	0.000371	0.002653	0.00539	0.04120	36362.	538.	178038.
50-54	150.000	0.0000168	0.000828	0.003565	0.00834	0.06170	34864.	742.	168884.
55-59	170.000	0.0000168	0.001322	0.004523	0.01369	0.09305	32713.	911.	155829.
60-64	190.000	0.0000168	0.002192	0.005953	0.02084	0.13491	29664.	1125.	138094.
65-69	200.000	0.0000168	0.002751	0.006825	0.03193	0.18741	25666.	1110.	115888.
70-74	200.000	0.0000168	0.003821	0.008171	0.04814	0.25967	20856.	1080.	90062.
75-79	200.000	0.0000168	0.003850	0.008208	0.07570	0.35518	15440.	753.	62441.
80-84	200.000	0.0000168	0.003948	0.008331	0.11794	0.47853	9956.	449.	36586.
85-99	200.000	0.0000168	0.002197	0.006128	0.21587	1.00000	5192.	143.	23158.
TOTALS								8144.	2124690.
NON-SMOKERS AND SMOKERS COMBINED								14816.	5389152.

TABLE L.4

TABLE L.4

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: ABSOLUTE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT MULTIPLICATIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	EXCESS	OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON -YEARS
NON-SMOKERS									
15-19	10.000	0.0000027	0.000000	0.000027	0.00168	0.00849	60000.	8.	248726.
20-24	30.000	0.0000027	0.000001	0.000081	0.00206	0.01068	59491.	24.	245863.
25-29	50.000	0.0000027	0.000003	0.000133	0.00151	0.00821	58856.	40.	243069.
30-34	70.000	0.0000027	0.000007	0.000184	0.00158	0.00882	58374.	56.	240575.
35-39	90.000	0.0000027	0.000047	0.000205	0.00228	0.01260	57858.	72.	287462.
40-44	110.000	0.0000027	0.000165	0.000160	0.00339	0.01841	57128.	92.	283005.
45-49	130.000	0.0000027	0.000371	0.000042	0.00539	0.02860	56077.	114.	276355.
50-54	150.000	0.0000027	0.000828	-0.000288	0.00834	0.04345	54473.	144.	266403.
55-59	170.000	0.0000027	0.001322	-0.000648	0.01369	0.06930	52106.	170.	251393.
60-64	190.000	0.0000027	0.002192	-0.001323	0.02084	0.10286	48495.	200.	229777.
65-69	200.000	0.0000027	0.002751	-0.001765	0.03193	0.15175	43506.	198.	200574.
70-74	200.000	0.0000027	0.003821	-0.002662	0.04814	0.21846	36904.	190.	163558.
75-79	200.000	0.0000027	0.003850	-0.002686	0.07570	0.31908	28842.	134.	119732.
80-84	200.000	0.0000027	0.003948	-0.002769	0.11794	0.44877	19639.	87.	73987.
85-99	200.000	0.0000027	0.002197	-0.001300	0.21587	1.00000	10826.	45.	49941.
TOTALS								1578.	3380397.
SMOKERS									
15-19	10.000	0.0000380	0.000000	0.000380	0.00168	0.01024	40000.	76.	198975.
20-24	30.000	0.0000380	0.000001	0.001141	0.00206	0.01591	39591.	224.	196375.
25-29	50.000	0.0000380	0.000003	0.001903	0.00151	0.01694	38961.	368.	193150.
30-34	70.000	0.0000380	0.000007	0.002667	0.00158	0.02105	38301.	507.	189481.
35-39	90.000	0.0000380	0.000047	0.003477	0.00228	0.02863	37494.	651.	184775.
40-44	110.000	0.0000380	0.000165	0.004385	0.00339	0.03893	36421.	812.	178557.
45-49	130.000	0.0000380	0.000371	0.005404	0.00539	0.05430	35003.	983.	170219.
50-54	150.000	0.0000380	0.000828	0.006739	0.00834	0.07648	33102.	1204.	159099.
55-59	170.000	0.0000380	0.001322	0.008120	0.01369	0.10922	30571.	1363.	144346.
60-64	190.000	0.0000380	0.002192	0.009974	0.02084	0.15213	27232.	1527.	125517.
65-69	200.000	0.0000380	0.002751	0.011057	0.03193	0.20443	23084.	1425.	103196.
70-74	200.000	0.0000380	0.003821	0.012403	0.04814	0.27517	18369.	1274.	78532.
75-79	200.000	0.0000380	0.003850	0.012440	0.07570	0.36868	13314.	869.	53362.
80-84	200.000	0.0000380	0.003948	0.012563	0.11794	0.48944	8406.	505.	30599.
85-99	200.000	0.0000380	0.002197	0.010360	0.21587	1.00000	4292.	236.	18787.
TOTALS								12025.	2024945.
NON-SMOKERS AND SMOKERS COMBINED								13602.	5405342.

TABLE L.7g

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT ADDITIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL			PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON-YEARS
				LUNG CANCER EXCESS	**OTHER**				
NON-SMOKERS									
15-19	10.000	0.1246200	0.000000	0.000000	0.00168	0.00835	60000.	0.	298745.
20-24	30.000	0.1246200	0.000001	-0.000000	0.00206	0.01028	59499.	0.	295962.
25-29	50.000	0.1246200	0.000003	0.000000	0.00151	0.00755	58887.	1.	293324.
30-34	70.000	0.1246200	0.000007	0.000004	0.00158	0.00793	58443.	3.	291055.
35-39	90.000	0.1246200	0.000047	0.000046	0.00228	0.01182	57979.	27.	288181.
40-44	110.000	0.1246200	0.000165	0.000226	0.00339	0.01873	57294.	111.	283780.
45-49	130.000	0.1246200	0.000371	0.000658	0.00539	0.03159	56221.	285.	270641.
50-54	150.000	0.1246200	0.000828	0.001802	0.00834	0.05340	54445.	697.	264889.
55-59	170.000	0.1246200	0.001322	0.003408	0.01364	0.08799	51538.	1162.	240177.
60-64	190.000	0.1246200	0.002192	0.006533	0.02084	0.13747	47003.	1406.	218469.
65-69	200.000	0.1246200	0.002751	0.008752	0.03193	0.19520	40544.	2096.	182218.
70-74	200.000	0.1246200	0.003821	0.012156	0.04814	0.27427	32630.	2230.	139581.
75-79	200.000	0.1246200	0.003850	0.012248	0.07570	0.36808	23680.	1528.	94949.
80-84	200.000	0.1246200	0.003948	0.012560	0.11794	0.48944	14964.	899.	54474.
85-99	200.000	0.1246200	0.002197	0.006989	0.21587	1.00000	7640.	312.	33948.
TOTALS								11260.	3262389.
SMOKERS									
15-19	10.000	0.1246200	0.000000	0.000000	0.00168	0.00835	40000.	0.	199163.
20-24	30.000	0.1246200	0.000001	0.000002	0.00206	0.01029	39666.	1.	197308.
25-29	50.000	0.1246200	0.000003	0.000007	0.00151	0.00758	39258.	2.	195545.
30-34	70.000	0.1246200	0.000007	0.000014	0.00158	0.00800	38960.	5.	194022.
35-39	90.000	0.1246200	0.000047	0.000144	0.00228	0.01230	38648.	37.	192052.
40-44	110.000	0.1246200	0.000165	0.000572	0.00339	0.02043	38173.	139.	188908.
45-49	130.000	0.1246200	0.000371	0.001436	0.00539	0.03535	37393.	332.	183641.
50-54	150.000	0.1246200	0.000828	0.003538	0.00834	0.06158	36071.	763.	174744.
55-59	170.000	0.1246200	0.001322	0.006180	0.01364	0.10054	33850.	1205.	160591.
60-64	190.000	0.1246200	0.002192	0.011129	0.02084	0.15701	30447.	1864.	139942.
65-69	200.000	0.1246200	0.002751	0.014520	0.03193	0.21808	25666.	1965.	113764.
70-74	200.000	0.1246200	0.003821	0.020167	0.04814	0.30277	20069.	2021.	84242.
75-79	200.000	0.1246200	0.003850	0.020320	0.07570	0.39308	13993.	1331.	55073.
80-84	200.000	0.1246200	0.003948	0.020838	0.11794	0.51014	8492.	752.	30354.
85-99	200.000	0.1246200	0.002197	0.011596	0.21587	1.00000	4160.	260.	18114.
TOTALS								10666.	2127458.
NON-SMOKERS AND SMOKERS COMBINED								21926.	5389847.

OCCUPATIONAL EXPOSURE TO 4 WLM/YR FROM AGE 15 TO 64
METHOD OF PROJECTION: RELATIVE RISKS PER UNIT DOSE CONSTANT WITH AGE
EXPOSURE ACCUMULATED FROM FIRST TO LAST INCREMENT
SMOKING AND RADIATION INTERACT MULTIPLICATIVELY

AGE GROUP	TOTAL DOSE	RISK INDEX	DEATH RATES LUNG CANCER NATURAL	DEATH RATES LUNG CANCER EXCESS	DEATH RATES OTHER	PROBABILITY OF DYING	ALIVE AT START	LUNG CANCER DEATHS	PERSON-YEARS
NON-SMOKERS									
15-19	10.000	0.0201000	0.000000	0.000000	0.00168	0.00835	60000.	0.	298745.
20-24	30.000	0.0201000	0.000001	-0.000001	0.00206	0.01027	59499.	0.	295963.
25-29	50.000	0.0201000	0.000003	-0.000002	0.00151	0.00754	58887.	0.	293378.
30-34	70.000	0.0201000	0.000007	-0.000004	0.00158	0.00789	58444.	1.	291066.
35-39	90.000	0.0201000	0.000047	-0.000026	0.00228	0.01147	57983.	6.	288249.
40-44	110.000	0.0201000	0.000165	-0.000080	0.00339	0.01723	57318.	24.	284114.
45-49	130.000	0.0201000	0.000371	-0.000155	0.00534	0.02765	56330.	60.	277139.
50-54	150.000	0.0201000	0.000828	-0.000242	0.00834	0.04343	54773.	144.	267875.
55-59	170.000	0.0201000	0.001322	-0.000389	0.01369	0.07055	52394.	238.	252616.
60-64	190.000	0.0201000	0.002142	-0.000488	0.02084	0.10660	48698.	392.	230266.
65-69	200.000	0.0201000	0.002751	-0.000524	0.03193	0.15700	43507.	445.	199971.
70-74	200.000	0.0201000	0.003821	-0.000727	0.04814	0.22599	36676.	500.	161775.
75-79	200.000	0.0201000	0.003850	-0.000733	0.07570	0.32570	28388.	366.	117304.
80-84	200.000	0.0201000	0.003948	-0.000751	0.11794	0.45430	19142.	229.	77787.
85-89	200.000	0.0201000	0.002197	-0.000418	0.21587	1.00000	10446.	85.	47993.
TOTALS								2492.	3378788.
SMOKERS									
15-19	10.000	0.0201000	0.000000	0.000000	0.00168	0.00835	40000.	0.	199163.
20-24	30.000	0.0201000	0.000001	0.000003	0.00206	0.01029	39666.	1.	197308.
25-29	50.000	0.0201000	0.000003	0.000011	0.00151	0.00760	39258.	3.	195543.
30-34	70.000	0.0201000	0.000007	0.000031	0.00158	0.00806	38959.	7.	194011.
35-39	90.000	0.0201000	0.000047	0.000251	0.00228	0.01283	38645.	57.	191984.
40-44	110.000	0.0201000	0.000165	0.001031	0.00339	0.02268	38149.	226.	188576.
45-49	130.000	0.0201000	0.000371	0.002656	0.00534	0.04122	37284.	553.	182553.
50-54	150.000	0.0201000	0.000828	0.006679	0.00834	0.07620	35748.	1290.	171838.
55-59	170.000	0.0201000	0.001322	0.011863	0.01369	0.12574	33024.	2037.	154505.
60-64	190.000	0.0201000	0.002142	0.021661	0.02084	0.20026	28871.	3086.	129364.
65-69	200.000	0.0201000	0.002751	0.028433	0.03193	0.27063	23090.	3087.	99006.
70-74	200.000	0.0201000	0.003821	0.034442	0.04814	0.36644	16841.	2927.	67580.
75-79	200.000	0.0201000	0.003850	0.034792	0.07570	0.44938	10661.	1752.	40142.
80-84	200.000	0.0201000	0.003948	0.040805	0.11794	0.55668	5870.	899.	20085.
85-89	200.000	0.0201000	0.002197	0.032707	0.21587	1.00000	2602.	264.	10008.
TOTALS								16193.	2042459.
NON-SMOKERS AND SMOKERS COMBINED								18685.	5421247.

TABLE L.8

LIFE TABLE CALCULATIONS FOR ^{224}Ra INDUCED BONE SARCOMAS

UNDER THE CURRENT ABSOLUTE RISK MODEL

Exposure pattern: 1500 Bq per year oral intake of ^{224}Ra from birth to age 15
3000 Bq per year and intake of ^{224}Ra from age 15 to death

Age Range	Oral intake[1] (μCi/yr)	Percent absorbed to the blood[2]	Percent deposited in bone[2]	Skeletal mass[2] (g)	Average skeletal dose[3] (mrad/yr)	Risk coefficient[2] (sarcomas/10^5 rad)	Sarcoma rate[4] (sarcomas/10^5PY)	Years at Risk[2]	Cumulative Risk (sarcomas/10^5 PY)
1-15	0.0405	80	60	3500	39.36	20	0.787	15	11.81
16-20	0.0810	50	40	7000	16.40	15	0.246	5	1.23
21+	0.0810	20	20	7000	3.28	10	0.032	53	1.74
Total									14.78

[1] (3000 Bq/yr) (2.7 x 10^{-5} μCi/Bq) (body mass/70 kg)

[2] See text for origin of these assumptions

[3] (Intake in μCi/yr) (absorption) (deposition) (7086 rad-g/μCi)/(skeletal mass in g) where 7086 rad-g/μCi = (16.7 x 10^9 atoms ^{224}Ra/μCi) (26.5 MeV/atom) (1.6 x 10^{-8} rad-g/MeV)

[4] (Risk coefficient in sarcomas/rad) (average skeletal dose in rad/yr)

TABLE L.9

LIFE TABLE CALCULATIONS FOR ^{226}Ra and ^{228}Ra INDUCED CANCERS UNDER THE CUMULATIVE ABSOLUTE RISK MODEL

Exposure pattern: 700 Bq per year oral intake of ^{226}Ra and ^{228}Ra over entire lifetime

Age Range	Number living at start of interval	Cumulative systemic intake[1] (μCi)	Five-year risks of death per 10^5 persons			Radium-induced cancer deaths[4]
			bone sarcoma[2]	head carcinoma[3]	total	
0-4	100,000	:009	0.0	0.0	0.0	0.0
5-9	100,000	.028	0.1	0.0	0.1	0.2
10-14	100,000	.047	0.3	0.1	0.4	0.4
15-19	100,000	.066	0.6	0.3	0.8	0.8
20-24	99,165	.085	0.8	0.5	1.2	1.2
25-29	98,145	.104	1.0	0.7	1.7	1.6
30-34	97,405	.123	1.2	0.8	2.1	2.0
35-39	96,634	.142	1.4	1.0	2.5	2.4
40-44	95,514	.161	1.7	1.2	2.9	2.8
45-49	93,831	.180	1.9	1.4	3.3	3.0
50-54	91,166	.198	2.1	1.6	3.7	3.4
55-59	87,079	.217	2.3	1.8	4.1	3.6
60-64	80,782	.236	2.6	2.0	4.5	3.6
65-69	71,995	.255	2.8	2.2	4.9	3.5
70-74	60,533	.274	3.0	2.3	5.3	3.2
75-79	46,684	.293	3.2	2.5	5.8	2.6
80-84	31,364	.312	3.5	2.7	6.2	2.0
85+	17,077	.331	3.7	2.9	6.6	1.2
Total						37.6

[1] Cumulative systemic intake at midpoint of interval = (700 Bq /yr) (2.7 x 10^{-5} μCi/Bq) (midpoint years) (20% absorption)

[2] (2.36 x 10^{-5} sarcomas/PY - μCi) (cumulative intake lagged 5 years) (5 year interval)

[3] (1.96 x 10^{-5} carcinomas/PY-μCi) (cumulative intake lagged 10 years) (5 year interval)

[4] (Total radium-cancer 5-yr risk) (number living at start)

APPENDIX M

EFFECTS OF LATENCY ON PROJECTIONS OF RISK ESTIMATES BEYOND THE END OF FOLLOW-UP

M.1 INTRODUCTION

In using risk estimates derived from epidemiological data to set environmental standards, two forms of extrapolation may be required. First, the data in the dose range in which standards are to be set may be very limited, requiring extrapolaton by means of some dose-response model from the higher doses which most of the study subjects received; Appendix J dealt with this problem. Second, the period of observation may be terminated at a time when a sizeable proportion of the cohort is still alive, requiring assumptions about how excess risks will continue to accumulate in the future; the latter problem is the subject of this Appendix. To avoid confusion, the term "extrapolation" will be restricted to the dose-response problem and "projection" to the time problem.

The problem of projection in time is particularly difficult for diseases which have a long "latent period" (interval between exposure and death) and for exposures which are also extended over time. Lung cancers in miners are a classic example of both complications. The next section offers a few general principles and considers the kind of results which are commonly presented in the epidemiologic literature.

Section 3 describes a small simulation of various methods of projection under two models of latency. Section 4 provides a general method of analysis and projection which could be applied if raw data on individuals' exposure histories were available, and illustrates the approach using data on lung cancer in Quebec asbestos miners. Finally, Section 5 proposes a set of procedures which would make maximum use of grouped data in its published form and which would allow a quantitative estimate of the reliability of the projection.

M.2 GENERAL PRINCIPLES

Let us suppose that a subject's exposure is fractionated over an interval of time (T_0,T_1), so that at a particular instant t he was exposed to concentration c(t). Now let us define the biological latent period (BLP) as the interval $d=t_1-t_0$ between some increment of exposure t_0 and an elevation of the risk of some disease attributable to that increment of exposure at some later time t_1. The BLP is thus not a single quantity but a random variable having some distribution f(d). This distribution is not easily estimable from cohort studies, so a simple epidemiologic latent period (ELP), defined as the interval $D=T_2-T_0$ between first exposure, T_0, and death from the cause of interest, T_2, in those who have died by the end of the study, T, is commonly reported. As this quantity also varies between subjects, it can also be described by a distribution g(D;T). However, it is important to realize that the two distributions f(d) and g(D;T) are quite different (En73). On one hand, D may overestimate d because it is measured from the earliest rather than some average exposure time. On the other hand, D may underestimate d because it is "right censored" by the termination date of the study, by competing causes of death, and by loss to follow-up. Furthermore, the distribution g(D;T) may include a high proportion of cases which were not attributable to the specific exposure under study. Finally, the use of g(D;T) can lead to misleading conclusions when studying the effects on the latent period distribution of total dose or age at start, as these variables are related to the censoring pattern.

These limitations of the ELP are well illustrated by a study of mortality in a cohort of Newfoundland fluorspar miners exposed to radon daughters (dV80). The authors provide a distribution of ELPs broken down by year of first employment (Figure 7.3). Obviously those first employed more recently would be more heavily right censored, but even the group first employed 1933-1941 and followed till the end of 1971 would have been observed only 30 to 39 years. If entry to the cohort were uniformly distributed, the ELP interval 30-34 years would be 28% censored and the 35-39 year interval 82% censored. Adjusting the observed distributions accordingly, the number of new cases still declines after 25 years but nowhere near as rapidly. For the subcohort first employed 1942-50, the adjusted number of new cases is still rising in the 25-29 year interval. Combining the two subcohorts (weighted according to the presumed man-years in view), produces the distribution indicated on the figure, for which the median would be 25.6 years. In contrast, the authors examined a scatter diagram of age of death against age at first exposure and, finding a good fit to a slope of 1, concluded that the ELP was independent of age at first exposure and had a mean of 22.6 years. Further regression analyses failed to show an effect of either age at first exposure or average dose rate. In this regard, they differ from other authors (Jo76, Dr67) who have found such relationships. However, these findings are largely uninterpretable because of the complicated way ages, durations, and rates of exposure relate to the censoring pattern. For example, under the null hypothesis that the ELP is independent of all these factors, one would expect the ELP to be negatively related to age and year at start (because those first employed at older ages or more recently would be more heavily censored), positively related to duration and accumulated dose (because of the longer interval between first and average exposure and because a subject would have to survive longer to achieve a longer dose) and, if dose rates were declining over time, positively related to dose rate (since both ELP and dose rate are negatively related to year of exposure). Hence a failure to find a negative relationship of ELP with dose rate could be the result of failure to take account of these biases (which would act in a postive direction).

M.3 SIMULATION STUDY

In an effort to understand better the relationship between biologic and epidemiologic latent periods and the reliability of various methods of projection in the presence of latency, a small simulation study has been carried out. The basic structure of the simulation is similar to that of Kn73, but differs in the details of the specification of the latency model and in the outcome measures examined. The present simulation sought to answer the questions:

1. Assuming an exposure of constant intensity over some period of time and a fixed BLP distribution, what is the resulting ELP distribution and how does it depend on exposure and censoring parameters?
2. If follow-up is terminated before 100% mortality occurs and the attributable and relative risks observed during the study period are projected forward in time, how accurately do these projections predict the final mortality experience of the cohort?

The simulation was carried out as follows. Two cohorts are defined, both of which are exposed to a constant small background rate of carcinogen (arbitrarily set to 1) for their entire lifetime; one cohort is additionally exposed to a C-fold higher concentration of carcinogen between ages T_0 and T_1; these cohorts will be termed the "unexposed" and "exposed" cohorts (denoted by subscripts U and E) and the applied dose at time t will be denoted $c(t) = 1$ or C. Each cohort is then followed from time T_0 to extinction in a standard life table calculation with death rates for two causes of death, $\lambda_1(t,c(.))$ which depends on exposure as described below, and

$$\lambda_2(t) = \alpha_2 t^k \qquad [1]$$

which is independent of exposure. The choice of $\alpha_2 = 0.9\times10^{-12}$ and k=6 seemed to give a reasonable approximation to the population death rates, and these values were used for all simulations. The exposure-driven death rates $\lambda_1(t,c(.))$ were assumed to be the sum of a linear effect of each exposure increment, lagged by some distribution, i.e.

$$\lambda_1(T,c(.)) = \int_0^T \alpha_1\, c(t)\, f(T-t)\, dt \qquad [2]$$

The lognormal distribution was chosen for f(T-t) with median μ and logarithmic standard deviation σ, i.e.

$$f(d;\, \mu,\sigma) = \frac{1}{\sqrt{2\pi}\sigma d} \exp\left[- \frac{\ln^2(d/\mu)}{2\sigma^2} \right] \qquad [3]$$

To allow the possibility that the median latent period might depend on dose, the inverse power law (Jo76)

$$\mu = \beta\, C(T)^{\gamma} \text{ where } C(T) = \int_0^T c(t)\, dt \qquad [4]$$

was used. One of the difficulties of the latent period model is that to explain the continuing rise in cancer rates with age, it is necessary to assume a median latent period of more than 50 years, which is inconsistent with the experience of those heavily exposed (Ar60). Rather than add an independent effect of aging, equation [4] with $\gamma<0$ provides a solution to the dilemma. The leukemia incidence among the atomic bomb survivors and the ankylosing spondylitis patients and various animal studies all suggest a value of $\gamma = -1/3$. With $c = 30$, the choice $\beta = 200$ and $\gamma = -1/3$ produces a median latent period of about 30 years in the exposed cohort and about 60 years in the unexposed cohort (both varying slowly with age as $C(t)$ accumulates). Thus the excess risk would be largely finished before the entire cohort died if exposure ceased early enough. For comparison, $\beta = 70$ and $\gamma = 0$ (i.e. median latent period of 70 years in both cohorts, independent of accumulated dose) was chosen to produce an excess risk which would continue beyond the maximum survival of the cohort.. Thus the mortality experience of the two cohorts is completely specified by formulae 1-4, with the parameters as specified in the following table.

Parameter	Simulation 1	Simulation 2
α_2	0.9×10^{-12}	0.9×10^{-12}
k	6	6
α_1	.001	.001
c	30	30
(T_1, T_2)	(30,50)	(30,50)
β	200	70
γ	-1/3	0
σ	0.30	0.25

The projection of the total excess risk is carried out as follows. At age t, the probability of dying of cause 1 is

$$q_1(t) = \lambda_1(t)\, S(t) \text{ where } S(t) = \exp(- \int_{T_1}^{t} [\lambda_1(\tau)+\lambda_2(\tau)]\, d\tau) \qquad [5]$$

Then

$$Q_1(T) = \int_0^T q_1(t)\, dt$$

$AR=Q_{1E}(\infty) - Q_{1U}(\infty)$ is the increase in the lifetime probability of dying of causes attributable to exposure, which we shall take as the fundamental measure of risk to be estimated. Now suppose follow-up is terminated at age T. Over the study period, the average relative and attributable risks are estimated as

$$RR(T) = Q_1(T) \;/\; E_1(T) \qquad [6]$$

$$AR(T) = Q_1(T) - E_1(T) \qquad [7]$$

where

$$E_1(T) = \int_{T_0}^{T} \lambda_{1U}(t)\, S_E(t)\, dt = \int_{T_0}^{T} e_1(t)\, dt \qquad [8]$$

is the expected deaths in the exposed cohort based on the rates in the unexposed cohort. For projection, RR(T) and AR(T) need to be expressed per unit of accumulated exposure to the occupational dose, as follows

$$RRI(T)=[RR(T)-1]/C_E(T) \text{ where } C_E(T)=\frac{\int e_1(t)C(t)dt}{\int e_1(t)dt} \qquad [9]$$

$$ARI(T)=AR(T)/C_S(T) \text{ where } C_S(T)=\int S_E(t)C(t)dt \qquad [10]$$

Finally, these relative and absolute risks per unit of accumulated dose can be projected forward by applying them to the rates and man-years (respectively) in the unexposed cohortas follows

$$PR_{RR}(T) = RRI(T) \int_{T_0}^{\infty} \lambda_{1U}(t)\, S_U(t)\, C(t)\, dt \qquad [11]$$

$$PR_{AR}(T) = ARI(T) \int_{T_0}^{\infty} S_U(t)\, C(t)\, dt \qquad [12]$$

The ELP distribution censored at age T is simply

$$g(D) = q_1(T_0+D) \;/\; Q_1(T) \qquad [13]$$

and the mean of the ELP is

$$\bar{D}(T) = \int_{T_0}^{T} D\, g(D)\, dD \qquad [14]$$

which we wish to compare with the simulated BLP μ.

Figures M.1 and M.2 summarize the results for the two simulation models. Part A gives the death rates $\lambda_E(t)$. For both simulations the death rates are increasing functions of age in the unexposed cohort. In simulation 1, the death rates in the exposed cohort start to differ about 10 years after first exposure, peaks about 35 years after first exposure, and by age 100 has nearly returned to the unexposed cohort's rate. In simulation 2, the exposed rate begins to differ only about 30 years after first exposure and the difference is still increasing at age 100. Part B shows the instantaneous relative risk $\lambda_{1E}(t)/\lambda_{1U}(t)$ and the average relative risk RR(T) over the study period. In both simulations, the average RR lags behind the instantaneous, the difference increasing with age as the number of new deaths starts to decline. Finally part C gives the two of new deaths starts to decline. Finally part C gives the two projected risks as a function of the age at which observation is stopped. Obviously, as the period of observation reaches zero survival, the two methods of projection both converge to the true value. Under either latency model, both methods of projection will seriously underestimate the ultimate effect if follow-up is stopped too early, unless some adjustment for latency is made in the risk estimates (as discussed in Section M.4). In simulation 1, the relative risk projection model starts to overestimate the ultimate effect around the time the peak in instantaneous rates is reached, attaining a maximum overestimation at the maximum average relative risk. In both simulations, the AR projection model always underestimated the final effect, but the situations examined are not sufficiently exhaustive to establish this as a universal principle.

Figure M.3 contrasts the BLP and ELP distributions in the exposed cohorts under the two models. In both models, the two distributions differ in shape, scale and location. In simulation 1, the ELP starts to rise later than the BLP because it is defined from first rather than average exposure, a difference of 10 years. It also falls off more rapidly because of censoring by competing causes of death. The mean ELP is 34.5 years, which is within the range of median BLPs simulated (51.4 to 23.3). In simulation 2, the ELP starts to rise earlier because most of the early cases are attributable to the background rather than occupational exposure. Again it falls off faster because of censoring. Here the mean ELP is 39.1 years, which is nowhere near the simulated median BLP of 70 years.

M.4 METHODS OF ANALYSIS FOR RAW DATA

Methods of dose-response analysis for any particular measure of cumulative exposure are now well established (Th81a). Where that measure varies within an individual over time, all fully efficient methods can be seen as a comparison of each of the deaths against those at risk and in view at the time of death, where exposure is evaluated in deaths and survivors at the same point in time (Pr78). Thus essentially the same information can be obtained either from a cohort study or a case-control study where controls are sampled in a particular way (Li77).

However, very little attention has been paid to incorporation of latency into the measure of cumulative exposure. In lieu of a generally accepted model, most epidemiologists use an unweighted accumulation of concentrations, either up to the point of comparison (He76) or some arbitrarily fixed interval Δ before the point of comparison (Li77). The latter approach is certainly an improvement, as in the presence of latency the most recent exposure increments are unlikely to contribute anything but noise (thereby reducing the estimated slope) and will cause the slope per unit of dose to be further underestimated by overestimating the "effective dose". It is a better approach than eliminating deaths and man-years in the first few years, as we have done in reporting the findings for all of the mining data (Appendix K), because these are useful in better defining the baseline risk.

To avoid the arbitrariness in the choice of interval Δ up to which exposures are to be integrated, one could consider letting Δ be a parameter to be estimated by maximum likelihood. This is equivalent to postulating the latent period model of equation [2] in which f(d) is a uniform distribution starting at Δ and continuing throughout life. However, this is not a very sensible latent period distributoin and because of its discontinuity, Δ will be difficult to estimate. The lognormal distribution [3] is much more appealing and is commonly suggested in this context (Ar74). Thus, one would wish to estimate the three parameters α_1, μ, and σ (and perhaps γ as a test of the hypothesis that BLP depended on dose). This estimation can be done as a straightforward iterative search for the maximum likelihood. To reduce the computational burden, one can begin by examining the fit of the model for a range of initial choices of parameters. This is done in Table M.1 for the 215 Quebec asbestos lung cancer cases (to end 1973) and their matched controls (Li77, Th81a). Of the choices considered, a median of $\mu = 20$ provided the best fit for both smoking and asbestos. The fit to the smoking data was very little influenced by σ over the range 0.2 to 0.4, though the asbestos data fit best with the choice 0.4. Among the limited number of choices of μ with $\gamma = 1/3$, none fit better than $\gamma = 0$. None of these choices significantly fit better than an unweighted accumulation; indeed for asbestos, the unweighted index was best. Iterative searching for the MLE of the parameters (Th81b) provided only slight improvement in fit, with $\hat{\mu}=27.1$ years and $\hat{\gamma}=-0.26$ ($\chi_1^2 = 2.36$).

To illustrate further the effect of latency on projections over time, the unweighted index and the best fitting latency index $\mu = 20$, $\sigma = 0.4$, were fitted to estimate $\hat{\alpha}_1$ and the resulting relative risk model was used for projection using equation [11] with γ_{1U} and γ_{2U} as given by Quebec rates for 1973. (The absolute risk projection model [12] could not be used as the data fitted came from a case-control study.) The resulting projected risks for various patterns of asbestos exposure and smoking are given in Table M.2. Overall, the two exposure models produce fairly similar results, but their relativity depends on the particular exposure pattern. Thus, the latent period model is much more sensitive to when the dose occurs. Exposure at 15-19 years of age has only a minor effect because most of the latent period is past before the age at which most lung cancers occur. Conversely exposure at 60-64 has little effect because the latent period does not begin until after a sizeable proportion have died. At the intermediate ages, the latency index produces higher projections than the unweighted index. For lifetime exposures (the pattern likely to be of greatest interest for standard setting) the unweighted index produces a 37% higher projection than the latency index for asbestos and 4% higher for smoking.

It is important to emphasize that this cohort had been followed to ages 53 to 83 (depending on age of entry), so that 37% had already died, a substantially higher fraction than most of the studies of alpha radiation except for the Joachimsthal-Schneeburg miners. Thus, the differences in projections based on different indices might be much larger in other studies.

M.5 RECOMMENDATIONS

Few studies of alpha radiation have made any serious effort to take latency into account in providing risk estimates, though many provide descriptions of ELP distributions or breakdowns of risk by time since, age at, or year of first exposure. A notable exception is the study of US uranium miners (Lu71), for which an analysis exactly equivalent to that described in the previous section has been carried out. Individual exposure indices were calculated based on a lognormal distribution with μ = 5, 10, 15 and 25 years and σ = .405. With these indices, the attributable risk model was rejected because it greatly overestimated the risk at young ages. The fit of the relative risk model was evaluated by comparing observed and predicted cases for various breakdowns by year, time since, age at, and year of first exposure, and in each case, the 10 year median gave the best fit. This index was then used to project future deaths in the cohort and in a hypothetical population of 10,000 20-year olds entering employment now, under various assumptions about future exposure, using the method described above. The resulting projections (Table M.3) would be usable for standard setting in their present form, if one were willing to accept the model fitted (including the relative risk assumption, the linear dose-response assumption, and the 10-year median lognormal assumption).

For other studies, little can be done other than to project forward the excess relative and attributable risks per unit of accumulated dose provided by the authors. While many studies have offered ELP distributions, we have seen how these may differ considerably and unpredictably from the BLP, and even if one were willing to assume their equivalence, estimates of slope per unit of "effective dose" could only be computed by reference to raw data. One could consider redistributing the average excess risks RRI(T) or ARI(T) over time using the BLP distribution, but this could be seriously misleading if the BLP is heavily censored. For the Czechloslovakian miners, estimates of excess risk per unit of exposure, ARI(T), in three time intervals since first exposure (4-7, 8-11, 12+ years) are available (Ku79). These would allow refinement of projections in the early periods, but as the excess rates showed no signs of declining, they provide no help in projecting into the future; indeed if the peak occurs around 20 years, projecting the 12+ rate forward could seriously overestimate the ultimate effect.

It is distressing to be unable to come up with more positive recommendations. The best one can do in this situation is to report the ARP and RRP projections, hoping the truth lies in between, and to recommend strongly to investigators that they use more suitable statistical methods in reporting their findings than has normally been done.

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TABLE M.1

Significance of Prediction by the Latency Model with various Choices of Parameters

Model Parameters			Score Function Chi-Square with 1 d.f.	
			Asbestos Exposure	Smoking
μ	σ	γ		
5	.3	0	4.73	41.23
10	.3	0	11.95	41.69
20	.3	0	31.01	42.96
40	.3	0	26.51	36.09
80	.3	0	3.65	17.43
20	.2	0	27.17	42.88
20	.3	0	31.01	42.96
20	.4	0	33.53	42.77
40	.3	-1/3	0.90	40.61
160	.3	-1/3	26.19	42.25
640	.3	-1/3	2.90	9.12
Unweighted Δ = 0 years			35.21	39.47
Unweighted Δ = 7 years			35.82	—
Exponential washout $T_{1/2}$ = 5 years			—	41.15

TABLE M.2

Excess Lung Cancer Deaths per 1000 Persons by Age 90 Projected by the Relative Risk Model with Various Exposure Indices

Period of Exposure	Exposure Index	
	Unweighted Accumulation	20-year Latent Period
	Total Asbestos Exposure of 1000 mppcfy	
15-64	95.3	69.7
15-19	100.0	14.5
30-34	99.9	60.1
45-49	96.6	108.1
60-64	70.7	62.8
	Smokers of 20 cigarettes per day	
15-89	56.0	54.1
40-89	30.0	38.7
65-89	6.4	3.8
15-89	56.0	54.1
15-64	50.2	50.6
15-39	27.2	16.2
15-19	5.5	1.0
15-19	5.5	1.0
40-44	5.5	7.5
65-69	3.1	2.6

TABLE M.3

Projected number of survivors and of cumulative respiratory cancer deaths among 3 groups of 10,000 white males 20 years of age for selected future ages and annual levels of exposure

	Miners living in the four-state area					
	Exposure at 0 WLM per year		Exposure at 4 WLM per year		Exposure at 12 WLM per year	
Age	Number of survivors	Cumulative no. of RC deaths	Number of survivors	Cumulative no. of RC deaths	Number of survivors	Cumulative no. of RC deaths
20	10,000	0.0	10,000	0.0	10,000	0.0
25	9,879	0.0	9,879	0.0	9,879	0.0
30	9,793	0.0	9,793	0.0	9,793	0.0
35	9,714	0.82	9,713	1.81	9,712	2.82
40	9,601	2.39	9,598	5.82	9,594	9.34
45	9,418	8.60	9,404	22.46	9,390	36.62
50	9,130	20.96	9,095	55.87	9,060	91.52
55	8,654	46.34	8,586	117.08	8,513	192.28
60	7,928	94.15	7,814	215.46	7,692	345.95
65	6,918	164.66	6,789	315.18	6,649	477.18
70	5,792	245.74	5,674	404.93	5,546	576.17
75	4,473	307.65	4,379	467.72	4,278	639.90
80	2,963	352.89	2,900	512.48	2,833	684.11

Exposure was truncated at exact age 50 with risk of dying continued to age 80.

Reprinted from Lu71, Table 44.

FIGURE M.1
SIMULATION OF LATENT PERIOD MODEL

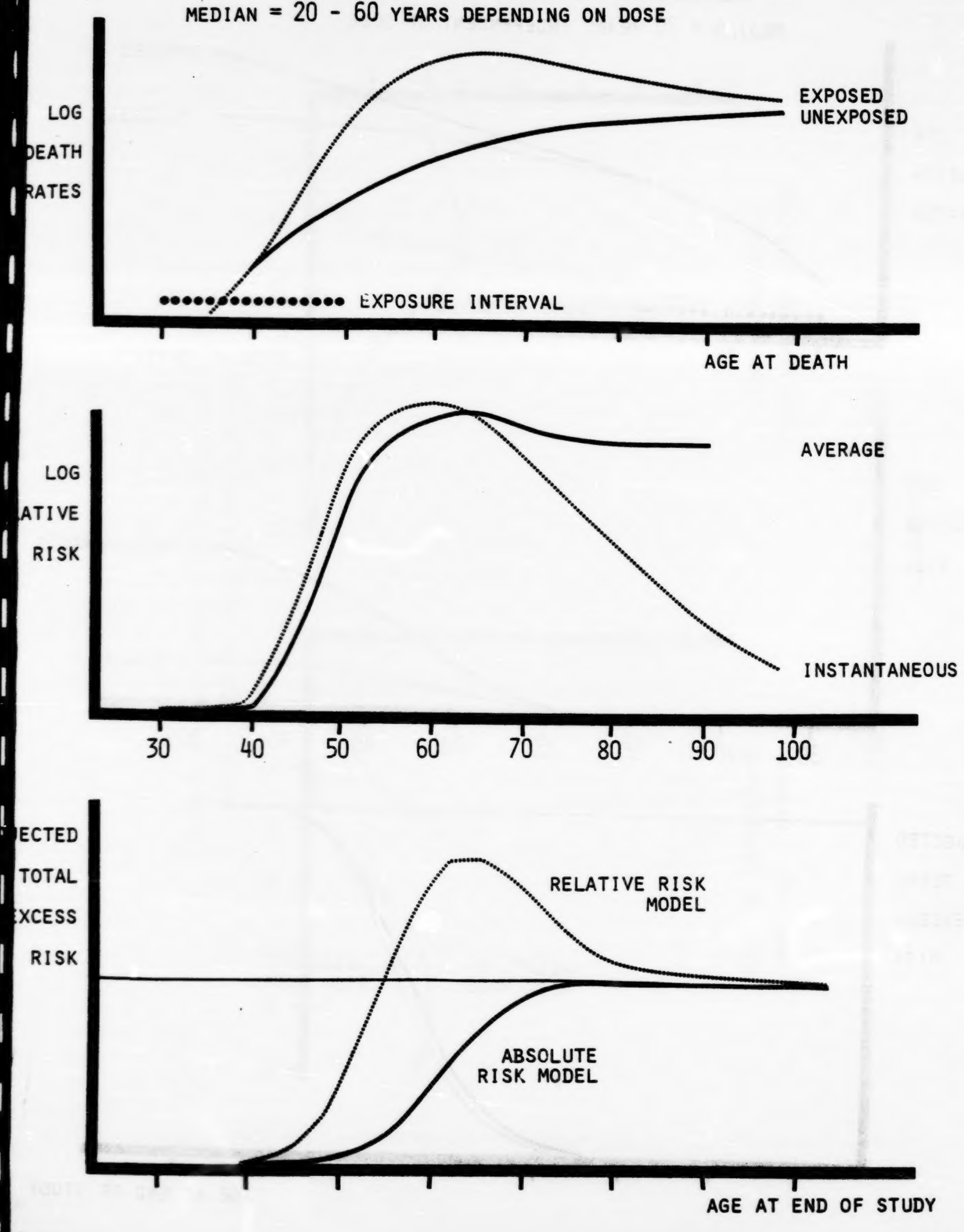


FIGURE M.2

SIMULATION OF LATENT PERIOD MODEL

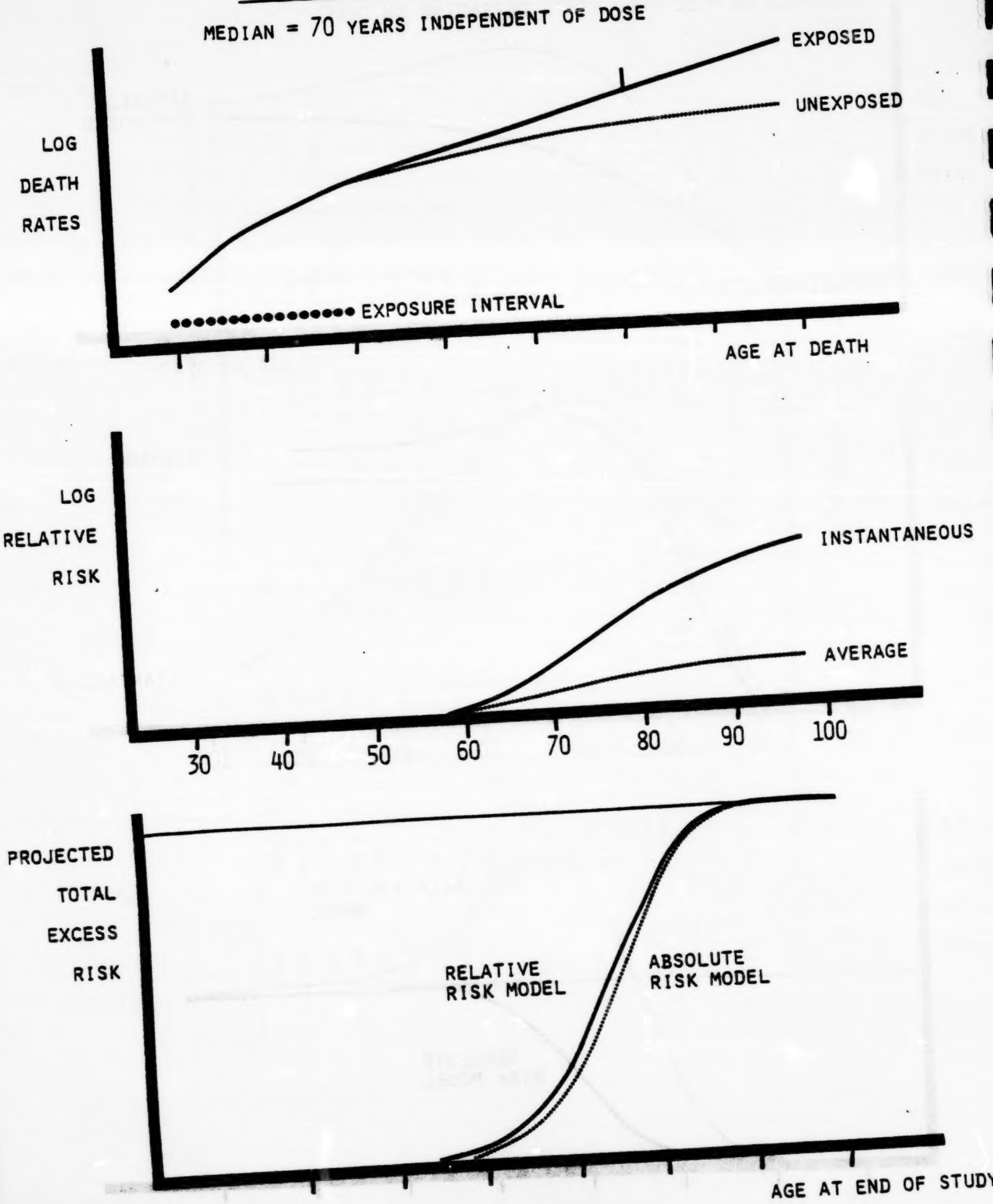
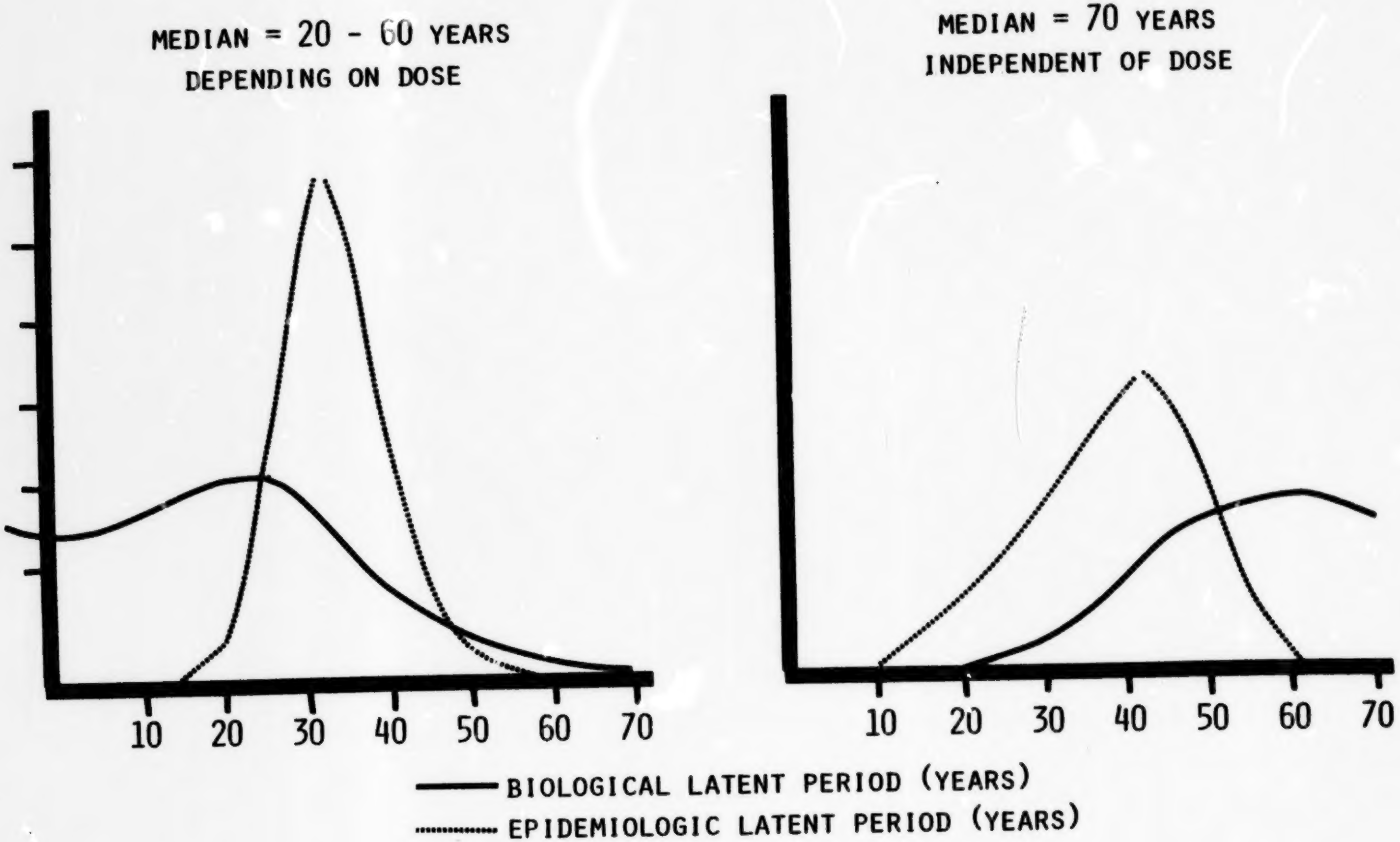


FIGURE M.3

SIMULATION OF LATENT PERIOD MODEL



POOR

QUALITY

ORIGINAL